Clinical outcome of intracoronary versus intravenous high-dose bolus administration of tirofiban in diabetic patients undergoing primary percutaneous coronary intervention

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Abstract

Background: Previous trials remain inconsistent regarding the advantages and hazards related to intracoronary (IC) compared with intravenous (IV) administration of thrombolytics. We aimed to evaluate the safety and effectiveness of IC versus IV tirofiban administration in diabetic patients (DM) with acute ST-segment elevation myocardial infarction (STEMI) during primary percutaneous coronary intervention (PCI).

Methods: This trial included 95 patients who were randomised to high-dose bolus plus a maintenance dose of tirofiban administered either IV or IC. The groups were compared for the incidence of composite major adverse cardiac events (MACE) at 30 days. Levels of cardiac markers were recorded pre- and post-intervention for myocardial perfusion.

Results: The MACE were not different between the groups, but post-procedure myocardial blush grade (MBG) 3 and thrombolysis in myocardial infarction (TIMI) 3 flow were significant in the IC group (p = 0.45, 0.21, respectively), favouring the IC strategy. Peak values of both creatine kinase-muscle/brain (CK-MB) and high-sensitivity troponin T (hs-TnT) were significantly lower in the IC group (155.68 ± 121, 4291 ± 334 ng/dl) versus the IV group (192.4 ± 86, 5342 ± 286 ng/dl) (p = 0.021, p = 0.035, respectively). The peak value was significantly lower in the IC group than the IV group in terms of ST-segment resolution and 30-day left ventricular ejection fraction (LVEF) (p = 0.016 and 0.023, respectively).

Conclusion: Thirty days post PCI, IC tirofiban was more efficient in ameliorating blood flow in the coronary arteries and myocardial tissue perfusion in DM patients after STEMI despite bleeding events, and MACE rates showed no significant difference between the groups. The IC group showed better improvement in LVEF.

Keywords: diabetes mellitus, STEMI, intracoronary tirofiban, primary coronary intervention

Impaired glucose metabolism accelerates the risk of arteriosclerosis and 80% of patients with diabetes mellitus (DM) die from cardiovascular diseases. Previous trials have demonstrated a positive correlation between hyperglycaemia and the occurrence of heart failure, arrhythmia and other complications. Moreover, hyperglycaemia significantly increased the mortality rate of patients with diabetes complicated by myocardial infarction (MI).

Acute occlusion of the major epicardial coronary artery usually leads to acute ST-segment elevation myocardial infarction (STEMI). Successful recanalisation and patency of the occluded vessels with percutaneous coronary intervention (PCI) or fibrinolytics diminishes the infarction size, saves the function of the ventricle and decreases morbidity and mortality rates.

Several consequences, such as no reflow and slow flow, associated with more major adverse cardiac events (MACE), complications and high mortality rates have been observed in patients with DM complicated by acute MI (AMI) and undergoing primary PCI. Platelet aggregation into the distal microvasculature or thrombus embolisation immediately after successful intervention impairs microvascular flow. Administration of glycoprotein IIb/IIIa inhibitors (GPI) and fibrinolytics diminishes the infarction size, saves the function of the ventricle and decreases morbidity and mortality rates.

American guidelines recommend tirofiban during PCI in patients with STEMI for high burden of thrombus or patients who received inadequate loading of P2Y12 inhibitors, and in patients with non-ST-elevation acute coronary syndrome...
(NSTE-ACS) and high risk. European guidelines recommend tirofiban use in PCI for bailout situations if there is angiographic evidence of massive thrombus, slow or no reflow, or thrombotic complications.10,11

This trial attempted to assess whether intracoronary (IC) administration of high-dose bolus plus a maintenance-dose infusion of tirofiban would lead to better efficacy and safety and enhance clinical outcomes better than the standard intravenous (IV) bolus-plus-infusion regimen during PCI for diabetic patients with acute STEMI.

Methods

The study evaluated 95 consecutive diabetic patients undergoing primary PCI for STEMI. Patients were recruited to receive 25 μg/kg tirofiban bolus plus a maintenance dose of 0.15 μg/kg/min infusion either IV (group A: n = 50) or IC (group B: n = 45) for 24 hours.

We included adult patients between 18 and 75 years with a clinical presentation of STEMI and specific ECG criteria in the form of ST-segment elevation ≥ 1 mm in two or more contiguous leads, except V2 and V3 had to be ≥ 1.5 mm in females, ST-segment elevation ≥ 2.5 mm in males less than 40 years or ≥ 2 mm in males more than 40 years, or the presence of new-onset or presumed new left bundle branch block.13

The institutional ethics committee approved the study and all patients signed informed consent.

Patients with marked uncontrolled hypertension (≥ 180/110 mmHg), rescue PCI and emergency coronary artery bypass grafting were excluded. Other exclusion criteria included patients presenting with cardiogenic shock, severe liver or kidney failure, bleeding diathesis, hypersensitivity or thrombocytopenia with tirofiban, platelets < 150 000 cells/mm³, active internal bleeding, history of ischaemic or haemorrhagic stroke within the last 30 days, atrioventricular malformation or aneurysm, neoplastic aortic dissection, acute pericarditis, haemorrhagic retinopathy and chronic haemodialysis.14

Before the intervention all patients were treated with acetylsalicylic acid (300 mg) and clopidogrel (600 mg). After securing vascular access through the right femoral or radial arteries, a total of 70–100 IU/kg unfractionated heparin IV bolus was given, then an additional weight-adjusted unfractionated heparin was given to achieve approximately 250 seconds of activated clotting time (ACT).

In both groups, a bolus of 25 μg/kg of tirofiban was given immediately after the guidewire crossed the lesion successfully and antegrade flow was restored, aiming to secure maximum concentration of the drug at the culprit lesion site and distal microvascular bed. A bolus dose of tirofiban was given through the guiding catheter in the infarct-related artery (IRA) at 30 seconds in the IC group. Maintenance IV tirofiban of 0.15 μg/kg/min for 18 hours was started in both groups after the bolus dose. An aspiration thrombectomy catheter was used if necessary and, finally, a suitable drug-eluting stent (FDA approved) was employed in the IRA in all patients.

Acetylsalicylic acid, a P2Y12 inhibitor (clopidogrel 75 mg), a high-intensity statin, beta-blocker and an angiotensin converting enzyme inhibitor or angiotensin II receptor blocker were prescribed as per the guidelines. When the activated clotting time (ACT) was < 160 seconds and/or four hours after anticoagulation, the vascular sheath was removed by manual compression.

The time to reperfusion was recorded from the onset of chest pain until the visualisation of at least thrombolysis in myocardial infarction (TIMI) 2 flow in the IRA during PCI. Before and after coronary intervention, TIMI flow grades15 and myocardial blush grade (MBG)16 were evaluated blindly by two interventional cardiologists. For evaluation of left ventricular ejection fraction (LVEF), the biplane modified Simpson’s method was used 48 hours after PCI and then again after 30 days.

The groups were compared for TIMI flow grades before and after the intervention, and MBG, maximum C-reactive protein (CRP) level, peak levels of both high-sensitivity troponin T (hs-TnT) and CK-MB, time to peak for hs-TnT and CK-MB, time to 50% ST resolution, and composite MACE rates at 30 days were recorded. Safety endpoints such as significant and minor bleeding and thrombocytopenia were noted.

According to the dye density, the MBG score was classified as grade 3 = normal myocardial contrast density compared to contrast density of a contra- or ipsilateral non-IRA, 2 = moderate myocardial blush where contrast density is less than that obtained from a contra- or ipsilateral non-IRA, 1 = minimal myocardial blush or contrast density, and grade 0 = no myocardial blush.16

MACE17 included cardiovascular death, recurrent myocardial infarction, stent thrombosis or target vessel revascularisation in hospitalisation at one month. Thrombocytopenia was defined as platelet count < 100 000 cells/mm³.18 Intracranial haemorrhage and decrease in haemoglobin concentration ≥ 5 g/dl were considered as major bleeding. Minor bleeding was defined as 10 to 15% decrease in haematocrit, blood loss with 3 to 5 g/dl decrease in haemoglobin concentration, or ≥ 4 g/dl decrease in haemoglobin concentration with no observed blood loss.18

Statistical analysis

Patients’ data were collected, revised and analysed using the statistical package for social sciences (SPSS) version 25.0 for windows (IBM Corp, Armonk, NY, USA). Data are presented as mean ± standard deviation (SD), frequency and percentage. Categorical variables were compared using the chi-squared (χ²) test. Continuous variables were compared with the Student’s t-test (two-tailed) and one-way ANOVA test for parametric data with Bonferroni post hoc test to detect differences between subgroups. The level of significance was accepted if the p-value was < 0.05.

Results

The two groups showed no statistically significant differences in cardiovascular risk factors, baseline characteristics or medication (Table 1). The mean age was 58.5 ± 10.18 years in the IV group and 55.90 ± 11.66 years in the IC group. The groups showed no significant differences in baseline level of glycated haemoglobin (HbA₁c) (p = 0.08), on-set-to-balloon and door-to-balloon times (p = 0.08, 0.3, respectively). Killip class frequency > 1 was 18% in group A (IV) and 24% in group B (IC) (p = 0.33) (Table 1).

Peak CK-MB value was significantly lower in the IC group than in the IV group (155.68 ± 121, 192 ± 86 U/l respectively) (p = 0.021). Peak hs-TnT value was significantly lower in the
were significant in the IC group \((p = 0.045, 0.021, \text{respectively})\). Comparison between the groups in terms of the culprit vessel affected and multivessel frequency showed no significant differences.

The incidence of MACE and major and minor bleeding during the hospital stay and at follow up are shown in Table 3. Only one patient developed major bleeding due to upper gastrointestinal bleeding. Five patients developed minor bleeding in group A (three patients developed access-site bleeding and two developed haematuria). In group B, one patient developed major bleeding in the lower gastrointestinal system and four developed haematuria.

### Discussion

Diabetic patients usually have microangiopathy and microvascular dysfunction. After restoration of normal blood flow in the coronary arteries, there is still insufficient myocardial tissue perfusion (i.e. no reflow and slow flow) in up to 30% of patients.\(^8,9\) Higher incidence of re-infarction, heart failure, stroke and death was previously documented in diabetic than in non-diabetic patients.\(^8\)

The main cause of slow flow and no reflow is thrombosis and microvascular embolisation. These microvascular complications are higher in AMI and primary PCI. Visible thrombus in coronary angiography can be removed by a suction catheter, but...
Loss of endothelium-dependent vasodilation, inflammatory reaction and platelet-dependent micro-thrombosis are enhanced by hyperglycaemia, thereby aggravating the perfusion disturbance of coronary microcirculation. The mortality rate was much higher in patients when MBG decreased to 0 to 1.30

To the best of our knowledge, this is the first study to demonstrate short-term outcomes and safety of IC injection of high-dose bolus tirofiban plus a maintenance IV, compared with IV tirofiban in diabetic patients with STEMI. We showed that IC tirofiban resulted in decreased inflammation in MI, which was evidenced by a significant reduction in peak CRP level. Previous studies have reported on the predictive value of CRP in determining the risk of future cardiovascular events.31,32 Other studies have documented a post-procedure CRP rise in relation to myonecrosis.33 The efficient inhibition of platelet aggregation by tirofiban led to inhibition of inflammatory mediators.26

In spite of no significant differences in bleeding events and MACE rates during the 30-day follow up after PCI, the IC tirofiban group showed an improvement in left ventricular function. However, we need large, long-term, multicentre, randomised trials to assess whether IC injection of tirofiban at the time of primary PCI improves clinical outcome in diabetic patients.

The results of this study have certain limitations. We used non-random selection of patients for IC tirofiban, the patient number was relatively small, and we evaluated IC tirofiban on STEMI but did not compare the effects in NSTE-ACS. Despite including elderly patients in the study, we did not compare major and minor bleeding incidence and platelet level reduction in different-aged populations. A possible improvement in clinical outcome could be observed with longer follow-up periods as left ventricular systolic function was improved.

**Conclusion**

IC tirofiban improved coronary blood flow and myocardial tissue perfusion effectively in diabetic STEMI patients during primary PCI. Improved LVEF was also observed 30 days post primary PCI. However, bleeding events and MACE rates showed no significant difference between the groups.

**References**


