Basuoni A, et al., J Cardiol Stud Res 2019, 4: 015
DOI: 10.24966/CSR-768X/100015

HSOA Journal of Cardiology: Study & Research

Research Article

Effect of Intra-Coronary (IC) Tirofiban Following Aspiration Thrombectomy on Infarct Size, in Patients with Large Anterior STEMI undergoing Primary PCI

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Abstract

Background/Aim:

Thrombus embolization during Percutaneous Coronary Intervention (PCI) in STEMI results in sub-optimal myocardial perfusion and increased infarct size. This study aimed to evaluate effect of Intra-Coronary (IC) delivery of bolus Tirofiban following aspiration thrombectomy on reduction of infarct size using cardiac Magnetic Resonance (cMR) in patients with large anterior STEMI undergoing primary PCI.

Patients and Methods

A Prospective single-blinded randomized controlled trial of 100 patients with large anterior STEMI was screened at 2 sites in one country (Egypt). Aspiration thrombectomy was performed in all patients using a 6 F aspiration catheter. Patients were randomized to IC Tirofiban (Study group) and no IC Tirofiban (control group). To ensure high intra-thrombus drug concentrations, Tirofiban was administered locally at the site of the infarct lesion via the aspiration catheter after flushing of the aspiration catheter well.

Results

Patients randomized to IC Tirofiban compared with no IC Tirofiban had a significant reduction of infarct size at 30 days (median, 15.451 gm - IQR, 17.404 gm - n = 50) vs (median, 43.828 gm - IQR, 49.599 gm - n = 50) P value = 0.002. There is no significant difference in MACCE at 90 days between patients received bolus IC Tirofiban and patients who did not receive (P value = 0.723).

Conclusion

In patients with large anterior STEMI presenting early after symptom onset and undergoing primary PCI, infarct size at 30 days was significantly reduced by bolus intracoronary Tirofiban delivered to the infarct lesion site followed aspiration thrombectomy but not by manual aspiration thrombectomy only.

Keywords: Aspiration thrombectomy; Infarct size; Tirofiban

Introduction

Myocardium Salvaging is the main objective of reperfusion therapy. As a result, infarct size is strongly consistent with mortality after acute ST-Segment Elevation Myocardial Infarction (STEMI) [1]. Myocardial recovery after primary PCI is often suboptimal despite restoration of TIMI 3 flow, in part due to thrombus embolisation which results in impaired micro-vascular perfusion and increased infarct size [2]. Hence, measuring infarct size after reperfusion therapy offers important prognostic utility. Laboratory measures of infarct size include biomarkers such as Creatinine Phosphokinase (CK), Lactate Dehydrogenase (LDH), and Troponin (Tpn) levels. While these tests are promptly available and can be obtained in the acute setting, they are unreliable in comparison to infarct size assessed by cardiac imaging [3]. Furthermore, myocardial Blush grade is an independent predictor for outcome in acute myocardial infarction patients treated with reperfusion therapy [4]. For measuring the infarct size in humans, cardiac MR (cMR) after injection of Gadolinium contrast agents is currently considered the reference standard [1]. Indeed, the technique offers high spatial resolution and corresponds excellently to histological necrosis. Two strategies were proposed to reduce embolization after primary PCI: Bolus intracoronary (IC) Tirofiban and manual thrombus aspiration [5]. Previous Studies showed conflicting data about whether (IC) glycoprotein IIb/IIIa or manual aspiration regarding infarct size reduction or clinical outcome improvement [6,7]. Providing the data above, we performed our study to evaluate effect of intracoronary delivery of bolus Tirofiban following aspiration thrombectomy on reduction of infarct size using cMRI in patients with large anterior STEMI undergoing primary PCI.

Patients and Methods

A Prospective single-blind randomised controlled trial was conducted between August, 2014 and November, 2015. 100 patients with STEMI were screened at 2 sites in one country (Egypt). 100 patients were randomised (computer based) into 2 groups, study and control groups. Procedural data for the patients assigned to the study group who received intracoronary Tirofiban vs the control group who did not receive Tirofiban pooled across the thrombectomy randomisation (Figure 1).

The study was approved by the institutional review board at each participating center, and all eligible patients signed informed and written consent. Patients 18 years and older of both genders with symptoms consistent with STEMI longer than 30 minutes duration and 1 mm or greater of ST-segment elevation in 2 or more contiguous leads

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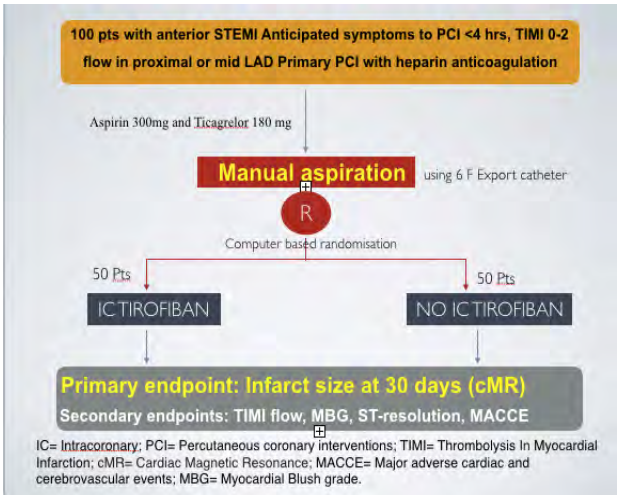
Citation: Basuoni A, El-Naggar W, El-Mahdy M, El-Kaffas S (2019) Effect of Intra-Coronary (IC) Tirofiban Following Aspiration Thrombectomy on Infarct Size, in Patients with Large Anterior STEMI undergoing Primary PCI. J Cardiol Stud Res 4: 015.

Received: July 18, 2019; **Accepted:** August 30, 2019; **Published:** September 6, 2019

in V1-V4, or new left bundle-branch block, with anticipated symptom-onset-to-device time of 6 hours or less (i.e., symptom-to-presentation time, 4 hours) were eligible for enrolment. Large acute Anterior STEMI defined by ECG showing at least 1 mm of ST- segment elevation in 2 or more contiguous leads in V1-V4, or new or presumably new) left bundle branch block. Infarct artery located in the proximal or mid Left Anterior Descending Artery (LAD), with TIMI 0/1/2 flow at the time of initial diagnostic angiography and based on coronary anatomy, PCI is indicated for revascularization.



Principal exclusion criteria included prior myocardial infarction, prior systolic dysfunction (ejection fraction < 40%), prior Coronary Artery Bypass Graft (CABG), previously stent implantation in LAD and in whom CA demonstrates stent thrombosis to be the cause of the AMI. As well as severe vessel tortuosity, diffuse disease or severe calcification is present which may impede successful delivery of aspiration device. Finally patients with Contraindication to cardiac Magnetic Resonance (cMR) were excluded.

Patients were loaded with dual antiplatelet regimen at time of presentation (Aspirin 300mg and Ticagrelor 180 mg). Adequate anticoagulation was done using IV un-fractionated heparin guided by ACT. All patients did diagnostic angiography to determine the culprit lesion, TIMI flow and any angiographic exclusion criteria. Guiding Catheter was placed then PTCA wire was placed distal to culprit lesion. Aspiration thrombectomy was performed in all patients using a 6 F Export Catheter. Patients were randamozied (computer based) to IC Tirofiban (Study group) and no IC Tirofiban (control group). The protocol specified actively aspirating whenever crossing the lesion or withdrawing the catheter, making several passes until no further thrombus or debris was retrieved. To ensure high intra-thrombus drug concentrations, a 25 mcq/kg bolus of Tirofiban was administered locally at the site of the infarct lesion via the aspiration device after flushing of the aspiration device well. Percutaneous coronary intervention was performed using standard techniques, with drug-eluting stents implantation. Assessment of final TIMI flow and myocardial blush were done by blinded observer. After PCI, all patients were treated with aspirin indefinitely and with Ticagrelor for at least 1 year. cMR and clinical follow up were scheduled for all patients at 30 days. The MRI studies have been read blindly to treatment allocation.

The cardiac MRI studies (by blind operator) were performed using 1.5 Tesla MRI machine with dedicated cardiac software, phased-array surface receiver coil, and electrocardiogram triggering. Breath-hold steady-state free-precession cine Cardiac MRI, T2-weighted imaging (edema imaging), 1st pass of contrast (perfusion study) and delayed myocardial enhancement using gadolinium (Gd-DTPA 0.2 mmol/kg) were performed. Off-line assessment of infarct mass as well as LVEF was done.

End Points and Definitions

Baseline patient data for demographic characteristics and medication use, presenting signs and symptoms, laboratory results, 12-lead electrocardiography, and coronary angiography were collected. The primary efficacy end point was infarct size (percentage of total left ventricular mass) at 30 days in patients assigned to intracoronary Tirofiban vs no Tirofiban (pooled across the thrombectomy randomization). Additional efficacy end points included measures of angiographic reperfusion (TIMI flow, Myocardial Blush Grade [MBG]), ST- Segment Resolution (STR) at 60 minutes. Cardiac MRI, angiographic, and STR end points were evaluated at independent core laboratories blinded to randomisation and outcomes. Major Adverse Cardiac and Cerebrovascular Events (MACCE) were defined as death, reinfarction, stroke, heart failure or clinically driven Target Vessel Revascularization (TVR). Bleeding was assessed using TIMI scales.

Statistical analysis

Statistical analysis was done using SPSS software. All continuous variables were tested against normality assumption. Data was expressed as percentage for discrete variables and mean values ± SD for normally distributed and medians [(with interquartile range (P25-P75)] for skewed data. Numerical differences between the two study groups were tested using non-parametric Mann-Whitney tests in skewed variables and Student's T test for normally distributed variables. Chi-square and Fisher's exact tests were used for comparison between the categorical variables. All p values were calculated using two-sided tests. Differences were considered statistically significant at $p < 0.05$.

Results

Between August, 2014 and November, 2015, 100 patients with STEMI were screened at 2 sites in one country (Egypt), 100 patients were randomised (parallel group randomisation) into 2 groups, study and control groups. The baseline characteristics of randmiozed groups were all matched (Table 1).

Procedural data for the patients assigned to the study group who received Intracoronary Tirofiban vs the control group who did not receive Tirofiban appeared in (Table 2). Manual aspiration was performed in all patients. Discharge medications included Aspirin, Ticagrelor, statins, Beta blockers and ACEIs in 100% of patients with no difference between the 2 groups.

Infarct Size

Evaluable cMRI results at 30 days were present in all patients randomised to intracoronary Tirofiban VS no intracoronary Tirofiban. Patients randomised to Intracoronary Tirofiban compared with no Tirofiban had a significant reduction in 30 days infarct size (median, 15.451 gm - IQR, 17.404 gm - n = 50) vs (median, 43.828 gm - IQR, 49.599 gm - n = 50) P value = 0.002 (Table 3).

Variables	Aspiration + IC Tirofiban	Aspiration + no IC Tirofiban	P -value
Age	52.2 ± 6.9	47.32 ± 7.4	0.02
Sex	38 (76%)	42 (84%)	0.48
Smoking	36 (72%)	34 (68%)	0.76
Diabetes Mellitus	22 (44%)	20 (40%)	0.77
Hypertension	8 (16%)	16 (32%)	0.19
Dyslipidemia	6 (12%)	6 (12%)	1
FH of CAD	4 (16%)	4 (16%)	1
Obesity	10 (20%)	4 (8%)	0.42
CKD	0	0	
LEAD	0	0	
Kilip class II	6 (12%)	6 (12%)	1
Prior MI or CABG	0	0	
Anterior MI	50 (100%)	50 (100%)	
Pain to door (hours)	median 4, IQR 2	median 4, IQR 2	0.99*
Door to balloon (minutes)	median 30, IQR 30	median 30, IQR 15	0.75*

Table 1: Baseline characteristics of the randomized groups.

Note: Data provided as mean ± standard deviation, median [interquartile range], or number [%]. IC = Intracoronary; FH= Family History; CAD = Coronary Artery Disease; LEAD = Lower Extremities Arterial Disease; MI = Myocardial infarction; CABG = Coronary Artery Bypass Graft.

Variables	Aspiration + IC Tirofiban n = 50	Aspiration + no IC Tirofiban n = 50	p- value
Proximal LAD artery	30 (60%)	28 (56%)	0.77
Mid LAD artery	20 (41.7%)	22 (45.8%)	0.77
Thrombus grade III	8 (16%)	4 (8%)	0.42
Thrombus grade IV	0	0	
Thrombus grade V	40 (80%)	46 (92%)	
Drug Eluting Stents	50 (100%)	50 (100%)	1
Number of stents	median 1, IQR 0	median 1, IQR 0	0.5*
stent length >30 mm	10 (41.7%)	7 (29.2%)	0.37
Radial approach	30 (60%)	29 (58%)	

Table 2: Procedural data for the patients.

Note: Data provided as mean ± standard deviation, median [interquartile range], or number [%]. IC = Intracoronary; LAD = Left Anterior Descending.

Variables	Aspiration + IC Tirofiban n = 50	Aspiration + no IC Tirofiban n = 50	p- value
Cardiac enzymes CKMB (TIME TO PEAK)	median 13.5, IQR 7	median 12, IQR 8	0.58*
ECG st. segment resolution post PCI	50 (100%)	50 (100%)	
ECHO (EF%)	median 46, IQR 13	median 40.5, IQR 16	0.13*
TIMI FLOW 3	44 (88%)	46 (92%)	1
Myocardial Blush grade 2/3	42 (84%)	46 (92%)	0.67
cMR infarction size gram (gm)	Median 15.451, IQR 17.404	Median 43.828, IQR 49.599	0.002 *
% Reduction of infarct size	Median 13.3, IQR 8.7	Median 25.45, IQR 24.4	0.002

Table 3: Myocardial perfusion and infarct size assessment.

Note: Data provided as mean ± standard deviation, median [interquartile range], or number [%].
IC = Intracoronary; CKMB = Creatine kinase-muscle/brain; PCI= Percutaneous coronary interventions; EF = Ejection fraction; TIMI=Thrombolysis In Myocardial Infarction; cMR = cardiac Magnetic Resonance

Myocardial Perfusion and ST-Segment Resolution

Post-PCI TIMI 3 flow, an MBG of 2 or 3, and complete STR at 60 minutes were achieved in 100% of patients. No significant differences in these measures were present between patients randomized to intracoronary tirofiban vs non IC tirofiban (Table 3).

Clinical outcomes

MACCE (defined as reinfarction, stroke, severe heart failure and death)) results at 90 days were present in 100 patents randomised to intracoronary Tirofiban VS no intracoronary Tirofiban. Patients randomised to intracoronary Tirofiban compared with no intracoronary Tirofiban had no significant reduction in MACCE results at 90 days, P value = 0.723 (Table 4). Bleeding risk (TIMI major and minor) and thrombocytopenia showed no difference between the 2 groups (Table 4). No significant differences in any of the major safety or efficacy end points were present between the randomized groups at 30 days (Table 4).

Variables	Aspiration + IC Tirofiban n = 50	Aspiration + no IC Tirofiban n = 50	p- value
MACCE	4 (8 %)	6 (12 %)	0.723
Heart failure	3	5	
Stroke	0	0	
Reinfarction	1	1	
Death	0	0	
Bleeding			
TIMI major	0	0	
TIMI minor	6 (12 %)	4 (8 %)	0.48
Thrombocytopenia	0	0	

Table 4: Clinical outcomes.

Note: Data provided as mean ± standard deviation, median [interquartile range], or number [%].

IC = Intracoronary; MACCE = Major Adverse Cardiac and Cerebrovascular Events; TIMI = Thrombolysis In Myocardial Infarction.

Discussion

For measuring the infarct size in humans, cardiac MR (cMR) after injection of Gadolinium contrast agents is currently considered the reference standard [1]. The principal findings from this trial in patients presenting early in the course of a large evolving anterior STEMI undergoing primary PCI are as follows: (A) bolus intracoronary Tirofiban delivered to the infarct lesion site followed aspiration thrombectomy significantly but modestly reduced the primary end point of infarct size at 30 days; (B) on contrary, manual aspiration thrombectomy alone did not reduce infarct size significantly and (C) indices of myocardial reperfusion, STR, and 30- days clinical event rates were not significantly different between the randomized groups. The present study was designed to maximise the likelihood that a reduction in infarct size could be demonstrated with intracoronary Tirofiban followed aspiration thrombectomy, if indeed such a reduction truly exists. Two of the strongest baseline determinates of infarct size are anterior MI location and abnormal TIMI flow [8].

We therefore limited enrolment of patients with proximal or mid LAD occlusion (and without prior MI) and operator assessed baseline TIMI 0-2 flow. We also restricted enrolment of patients who could be treated early, in whom the time window for effective myocardial

salvage had not closed [9]. Indeed, the median time from the onset of symptoms to hospital arrival was 4 hours, as well as the median door-to-device time was 30 minutes. Thus, the study population represents a highly selected cohort of patients with large anterior MI (those with the greatest clinical need), in whom infarct size reduction should be feasible given early presentation and rapid treatment.

We assessed infarct size by cMR, which strongly consistent with subsequent mortality [2,10]. To decrease sample size, prior studies using cMR have typically measured infarct size early after reperfusion (2-7 days), a period during which substantial myocardial edema is present that may be mischaracterised as non-viable myocardium [11,12]. We therefore powered the present trial for assessment of the primary infarct size end point at 30 days (when much of the myocardial edema has resolved), a time more specific for identification of truly infarcted myocardium [11].

Myocardial reperfusion was assessed by several complementary parameters, including post-PCI TIMI flow, MBG, and STR [13]. Despite of using heparin as the procedural anticoagulant in addition to intracoronary Tirofiban, there was no significance in the major and minor bleeding risks. These results need to be placed in the context of previous studies. Two earlier randomized trials demonstrated infarct size reductions with intracoronary compared with intravenous glycoprotein IIb/IIIa receptor antagonist (despite enrolment of patients with nonanterior MI presenting up to 12 hours after symptoms) [14,15]. And a meta-analysis of 6 randomized trials (1246 patients) reported enhanced survival with intracoronary abciximab [16]. However, the recently completed AIDA STEMI trial, which with 2065 randomised patients was powered for clinical outcomes, found nearly identical rates of MACE (and biomarker-assessed infarct size) with bolus intracoronary and intravenous abciximab [17]. In contrast to INFUSE AMI trail which used bivilurdin as the procedural anticoagulant without routine intravenous glycoprotein IIb/IIIa receptor antagonist [18], we used heparin in our trial as many studies have suggested that infarct size might be reduced by adding intravenous glycoprotein IIb/IIIa receptor antagonist and heparin [19]. However, in addition to enrolling only anterior STEMI patients presenting early, except for INFUSE AMI trial, all prior trials (including AIDA-STEMI), intracoronary glycoprotein IIb/IIIa receptor antagonist was infused proximally through the guide catheter, limiting its penetration into occlusive thrombus and allowing preferential drug flow to lower resistance pathways (such as the left circumflex artery) and blowback into the aorta. In contrast, the local drug delivery through the aspiration device used in our present study directly achieves high intraclot concentrations of glycoprotein IIb/IIIa receptor antagonist at the site of LAD occlusion, which may enhance platelet disaggregation and thrombus resolution [20,21]. In the present study, glycoprotein IIb/IIIa receptor antagonist bolus delivered directly to the infarct lesion site reduced infarct size at 30 days (the primary end point of the study) in patients with anterior STEMI reperfused early. The local drug delivery through the aspiration device after thrombus aspiration might decrease the chance of mechanically dislodged thrombus downstream while using clear way catheter in INFUSE AMI trial, perhaps explaining why infarct size was lowest in the combined aspiration/abciximab group of INFUSE AMI trial.

Regarding aspiration thrombectomy, in TAPAS, 1071 patients with anterior and nonanterior STEMI who presented within 12 hours of symptom onset at a single center were randomized to manual aspiration vs no aspiration before primary PCI; aspiration resulted in modest improvements in MBG and STR but a marked reduction in 1-year mortality [7,22]. Other trials of manual aspiration thrombectomy have reported conflicting results [23,24]. And in contrast to single-center studies, multicenter aspiration trials (TASTE 2013 and TOTAL 2015) have largely been negative [25]. Moreover, in TAPAS, aspiration did not reduce infarct size as measured by cardiac biomarkers [7], calling into question the mechanism underlying the survival benefit. In the present trial, in which only patients presenting early with anterior MI and coronary anatomy optimal for aspiration were enrolled, and in which cMRI was used to assess infarct size at 30 days, was specifically designed to overcome many of the limitations from these earlier studies. The fact that manual thrombus aspiration did not reduce infarct size in our study makes a substantial clinical benefit unlikely, questioning its routine use in STEMI.

Although infarct size at 30 days was reduced with intracoronary tirofiban group, early markers of microcirculatory reperfusion (MBG and STR) were not improved. This discordance may reflect different ascertainment times give infarct evolution over 30 days (especially as edema is substantially reduced during this time) and variable accuracy of different biomarkers. The comparable 90-day clinical event rates between groups is consistent with the early MBG and STR results [13,26].

Our study has several limitations. First, the trial was single-blind, with the operator knowing the randomisation assignment. Thus, while some bias cannot be excluded, the patient and follow-up personnel were unaware of the treatments provided, and the study used numerous core laboratories and a clinical events committee blinded to treatment assignment. Second, using of aspiration device as local drug delivery may have a risk of distal embolisation but there was no information about its hazardous before. Third, manual aspiration catheters with a larger internal diameter than the one used in the present trial are now available. However, studies have not shown greater thrombus retrieval or improved myocardial perfusion with larger bore devices [23]. Fourth, larger trials are required to determine whether the degree of infarct size reduction at 30 days achieved with intracoronary tirofiban with aspiration thrombectomy in the present study translates into improved late clinical outcomes without increasing bleeding.

Conclusion

In patients with large anterior STEMI presenting early after symptom onset and undergoing primary PCI, infarct size at 30 days was significantly reduced by bolus intracoronary Tirofiban delivered to the infarct lesion site followed aspiration thrombectomy but not by manual aspiration thrombectomy only. There is no significance in MACCE at 90 days between patients received Bolus intracoronary Tirofiban and patients who did not receive.

Acknowledgement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors report no financial relationships or conflict of interest regarding the content herein. The study was approved by the institutional review board at each participating center, and all eligible patients signed informed and written consent.

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Journal of Orthopedic Research & Physiotherapy

Journal of Otolaryngology, Head & Neck Surgery

Journal of Protein Research & Bioinformatics

Journal of Pathology Clinical & Medical Research

Journal of Pharmacology, Pharmaceutics & Pharmacovigilance

Journal of Physical Medicine, Rehabilitation & Disabilities

Journal of Plant Science: Current Research

Journal of Psychiatry, Depression & Anxiety

Journal of Pulmonary Medicine & Respiratory Research

Journal of Practical & Professional Nursing

Journal of Reproductive Medicine, Gynaecology & Obstetrics

Journal of Stem Cells Research, Development & Therapy

Journal of Surgery: Current Trends & Innovations

Journal of Toxicology: Current Research

Journal of Translational Science and Research

Trends in Anatomy & Physiology

Journal of Vaccines Research & Vaccination

Journal of Virology & Antivirals