Iranian Heart Journal; 2022; 23 (1)

Original Article

Comparison Between Intracoronary and Intravenous Eptifibatide and Intracoronary Reteplase in Patients Undergoing Primary Percutaneous Coronary Intervention: A Randomized Clinical Trial

Salman Nikfarjam[1], MD; Mostafa Zadkamali[1], MD; Arsalan Salari[1], MD; Maryam Shakiba[1], PhD; Mahboubeh Janesar Hoseinie[1], MD; Fardin Mirbolouk[1*], MD

ABSTRACT

Background: Despite the benefits of primary percutaneous coronary intervention (PPCI), myocardial perfusion after treatment remains disrupted in some patients. The utility of glycoprotein IIb/IIIa inhibitors and reteplase during the intervention is indeterminate.

Methods: We designed a randomized clinical trial to compare intravenous (IV) and intracoronary (IC) eptifibatide and reteplase in 144 patients with ST-elevation myocardial infarction scheduled for PPCI. The primary outcome was coronary blood flow according to the TIMI flow grade (TFG) before and after PPCI. The secondary outcomes were the differences between ST-segment resolution, diastolic left ventricular dysfunction, left ventricular ejection fraction, mitral regurgitation, CK-MB levels, and hemoglobin levels before and after PPCI.

Results: TFG III was achieved in all patients (100%) in the control and reteplase groups. TFG III was seen in 32 (88.9%) and 33 (91.7%) patients in the IV and IC eptifibatide groups, respectively. TFG II was reported in 4 (11.1%) and 3 (8.3%) patients in the IV and IC eptifibatide groups in the same order. Postprocedural TFG was not significantly different between the groups. There was a significant increase in the CK-MB level in the reteplase group compared with the other groups ($P<0.05$). Postprocedural hemoglobin, ST resolution, and ejection fraction were not significantly different between the groups. Reteplase was associated with a significant improvement in diastolic left ventricular dysfunction compared with the control group (odds ratio, 0.31; $P=0.02$). No difference was shown in the development of mitral regurgitation between the 4 groups.

Conclusions: Neither IV nor IC eptifibatide nor reteplase was associated with improvements in the coronary blood flow as determined by TFG, ST resolution, and ejection fraction.
(Iranian Heart Journal 2022; 23(1): 6-16)

KEYWORDS: Primary percutaneous coronary intervention, Eptifibatide, Reteplase, Intravenous, Intracoronary

[1] Cardiovascular Disease Research Center, Department of Cardiology, Heshmat Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, IR Iran.

*** Corresponding Author:** Fardin Mirbolouk, MD; Cardiovascular Diseases Research Center, Department of Cardiology, Heshmat Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, IR Iran.
Email: Mirboloukfardin@gmail.com **Tel:** +989116529538

Received: June 13, 2020 **Accepted:** September 11, 2020

Today, the world is facing an increased risk of myocardial infarction (MI) as a consequence of the growing incidence rate of coronary artery disease.[1,2] In the United States alone, annually, MI is diagnosed in about 1.5 million people, among whom ST-elevation myocardial infarction (STEMI) occurs in 24%.[3] Over the recent century, primary percutaneous coronary intervention (PPCI) has made a substantial revolution in the management of STEMI.[4] The complete establishment of the coronary blood flow is the main target of PPCI as the standard treatment method in these patients.[5] PPCI confers incremental benefits by comparison with fibrinolytic therapy; nonetheless, despite the return of the epicardial blood flow by PPCI, myocardial perfusion remains disrupted in up to 40% of patients with STEMI.[6] This finding is attributed to the embolization of coronary thrombi, causing the formation of microvascular clots, vasospasm, interstitial edema, and cellular damage.[7] This process interrupts blood flow in the myocardium and subsequently causes a reduction in the left ventricular (LV) function and poor clinical outcomes with increased in-hospital mortality rates.[8,9] In spite of the importance of this condition, there is currently no well-established medical treatment known to prevent impaired reperfusion. Many therapeutic strategies are adopted to improve microvessel perfusion after PPCI, including the mechanical prevention of distal embolization, the aspiration of thrombi, and the use of drugs such as glycoprotein IIb/IIIa inhibitors and fibrinolytic drugs during PPCI.[10,11] Nevertheless, there is no general agreement on the treatment choice. In fact, with the advent of newer technologies and the use of PPCI in more complex cases, the need for antiplatelets and fibrinolytics appears to be more serious.[12] Because glycoprotein IIb/IIIa inhibitors block the platelet aggregation process in the final stage, they are always considered an appropriate choice for preventing platelet accumulation and thrombus formation.[13] The use of glycoprotein IIb/IIIa inhibitors is still recommended as class II in selected patients during PPCI.[14] Another issue that is gaining more and more attention in different studies is the route of administration for these drugs. Recently, an intracoronary (IC) bolus of glycoprotein IIb/IIIa inhibitors has been tested in numerous trials, with the rationale that using a highly localized drug in the coronary arteries, compared with systemic administration, may be associated with a 100-fold higher concentration in the epicardial artery, further increasing drug efficacy.[15] Moreover, adverse systemic effects such as brain hemorrhage and subsequent mortality may be prevented by local drug delivery. We now present the results of a randomized controlled trial comparing the effects of IC and intravenous (IV) eptifibatide and IC reteplase on the coronary blood flow in PPCI patients.

METHODS

This prospective randomized controlled trial was performed in Heshmat Hospital, Rasht, Guilan, from December 2017 through June 2018. The trial protocol was approved by the Ethics Committee of Guilan University of Medical Sciences (IR.GUMS.REC.1396.304). The study protocol was approved by the Iranian Registry of Clinical Trials (Registration No. IRCT20170925036401N2). This study was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all the participants before the study began.

Study Population

All patients with a first-time diagnosis of STEMI presenting within 12 hours from the onset of symptoms who were candidates for PPCI were eligible to participate.

Inclusion and Exclusion Criteria

The inclusion criteria were composed of typical ischemic chest pain lasting more than 30 minutes, ST-elevation exceeding 1 mm in at least 2 leads, MI not more than 12 hours from the onset, life expectancy not less than 6 months, age between 18 and 80 years, not having previous evidence of MI, not having contraindications for reteplase or eptifibatide, not having left bundle branch block, and not having used glycoprotein IIb/IIIa inhibitors during the preceding 2 weeks.

The exclusion criteria were comprised of rescue PCI after thrombolytic therapy, the need for emergency coronary artery bypass graft surgery, cardiogenic shock, atrial fibrillation, thrombolysis in myocardial infarction flow grade (TFG) III in primary angiography, and participation in another simultaneous interventional study.

Intervention

The patients were randomly assigned to 4 groups according to a series of block randomization numbers. Each group contained 36 patients. The participants were all blind to the treatment group assignments. All the patients received 325 mg of chewing aspirin plus 600 mg of a loading dose of clopidogrel, as standard care, prior to randomization and transfer to the catheterization room. In all the patients, the femoral approach was used for catheterization. In each of the 4 treatment groups, the insertion of stents was performed after balloon dilatation.

The patients in the control group underwent thrombus suction after the wiring of the culprit vessel before the stent was deployed.

In the IV eptifibatide group, thrombus aspiration was done after the wiring of the culprit vessel. The patients received 180 µg/kg of an IV bolus dose of eptifibatide before the stent was implanted. Afterward, the patients received 2 µg/kg/min of an infusion of eptifibatide over 18 hours.

In the IC eptifibatide group, aspiration thrombectomy was performed after the wiring of the culprit vessel; then, the patients received an IC bolus dose of 180 µg/kg of eptifibatide. IC eptifibatide was injected twice at a 10-minute interval through a thrombus suction catheter at the distal location to the culprit lesion before the stent was deployed.

The patients in the reteplase group underwent thrombus suction after the wiring of the culprit vessel and then received a dose of 6 mg of IC reteplase before stent deployment.

The primary outcome of this trial was defined as the coronary blood flow in all the groups based on the angiographic criteria of TFG before and after PPCI. The secondary outcomes were composed of ST-segment resolution from the baseline to 90 minutes after PPCI, the differences between the pre and postprocedural values of diastolic left ventricular dysfunction (DLVD), ejection fraction, mitral regurgitation, creatine kinase-muscle/brain (CK-MB) levels, and hemoglobin levels.

After the procedure, coronary angiograms were checked to evaluate TFG. TFG was drawn upon to evaluate blood flow in the coronary arteries. TFG is a standard system for grading blood flow in the coronary arteries, and it is determined by cardiologists during angiography. TFG consists of 4 grades: grade 0 represents lack of blood flow after the stenotic site and grade III means normal and complete perfusion after the stenotic site.

Twelve-lead electrocardiography was done in all the participants at the time of arrival and within 90 minutes after PPCI in the Cardiac Care Unit. The sum of ST resolution 40 milliseconds after the QRS complex (J point) was calculated in leads I, aVL, and V_1 to V_6 for anterior MI and leads II, III, aVF,

and V_5 and V_6 for non-anterior MI. Echocardiography was performed at the time of arrival and 3 to 4 days after PPCI by a single person. LV ejection fraction, DLVD, and mitral regurgitation were assessed before and after the procedure. The short-axis parasternal view was obtained at the basal, mid, and apical surfaces, as well as the 4, 3, and 2-chamber views. All the images were obtained at a frame rate of 60 to 90 frames per second. The levels of CK-MB and hemoglobin were checked in all the patients at baseline and 24 hours after the commencement of the treatment.

Statistical Analysis

STATA, version 13, was used to analyze the data. The Kolmogorov–Smirnov test was employed to assess normality in distribution and the χ^2 test or the Kruskal–Wallis test for comparing groups in terms of underlying variables. Logistic regression was applied to compare the effects of the intervention on the secondary outcomes (ie, DLVD and mitral regurgitation). Covariance analysis was applied for the other secondary outcomes (ie, ST resolution, ejection fraction, and the levels of CK-MB and hemoglobin). A cutoff point of 0.05 for statistical significance was presumed.

RESULTS

Baseline Characteristics

Randomization was carried out in 144 patients, all of whom completed the study (Fig. 1).

The demographic and clinical characteristics of the 4 study groups are presented in Table 1. There were no statistically significant differences between the 4 groups concerning age, sex, smoking status, and history of diabetes and hypertension. Except for ejection fraction and DLVD, all the remaining angiographic and diagnostic characteristics were similar between the 4 groups at baseline (Table 1). The mean ejection fraction in the IV eptifibatide group was significantly lower than that in the other groups (P=0.04). The severity of DLVD before PPCI in the control group was significantly lower than that in the other 3 groups (P=0.04).

Ventricular fibrillation during PPCI, as a probable adverse event, was noted in 2% (4 patients) of the participants belonging to the reteplase group, and they were well-treated with electroshocks.

Postprocedural TFG III was achieved in all (100%) the patients in the control and reteplase groups. TFG III was seen in 32 (88.9%) and 33 (91.7%) patients in the IV and IC eptifibatide groups, respectively. TFG II was reported in 4 (11.1%) and 3 (8.3%) patients in the IV and IC eptifibatide groups in the same order. Postprocedural TFG grades were not significantly different between the 4 groups (P=0.054) (Fig. 2).

The postprocedural quantitative outcomes were compared between the 4 groups using the analysis of covariance. All the outcomes were adjusted for the baseline values of the covariates. The results are shown in Table 2. There was a significant increase in the CK-MB level (from the baseline to 24 hours after PPCI) in the reteplase group as compared with the other groups (P<0.05).

The adjusted values of postprocedural hemoglobin levels, ST resolution, and ejection fraction were not significantly different between the 4 groups (Table 2). Ordinal logistic regression showed that reteplase was associated with a significant improvement in DLVD compared with the control group (odds ratio [OR], 0.31; P=0.02). This model showed no difference regarding the development of mitral regurgitation between the 4 groups. Table 3 presents the results of the adjusted OR for improving grades of DLVD and mitral regurgitation in the study groups.

All the patients were discharged in good health, and there were no reported side effects.

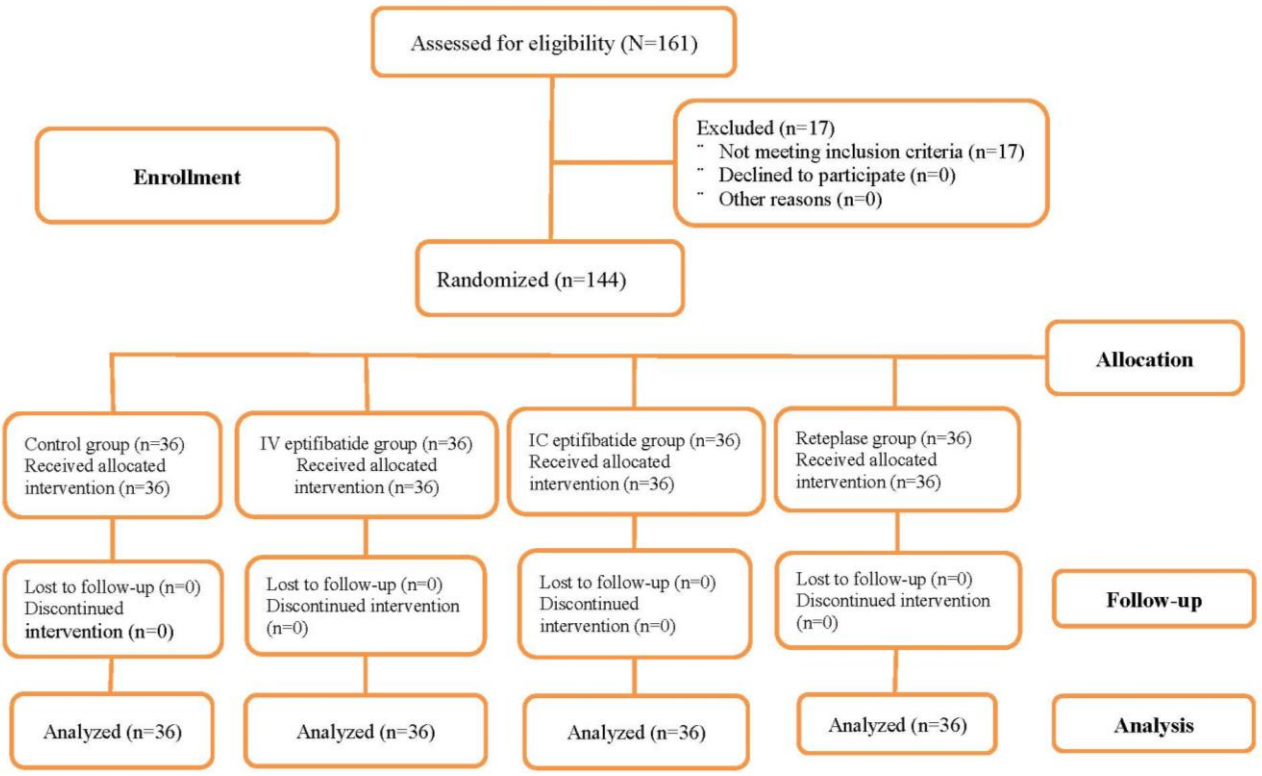

Figure 1. The image depicts the CONSORT flow diagram

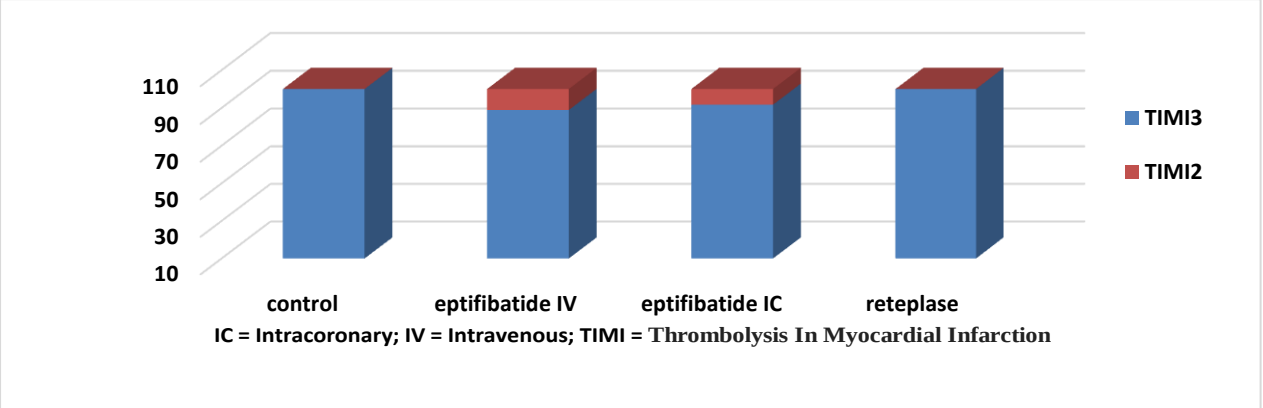

Figure 2. The image presents the postprocedural TIMI flow grade in the 4 study groups. TIMI, Thrombolysis in myocardial infarction

Table 1. Characteristics of the participants according to study groups

Participant Characteristics		Control Group	Intravenous Eptifibatide Group	Intracoronary Eptifibatide Group	Reteplase Group	*P*-value
Age mean(SD)		58.53(10.3)	57.94 (11.2)	58.89 (10.2)	58.25 (10.5)	0.98
Sex (number/percent)	Male	24 (67)	28 (78)	24 (67)	24 (67)	0.67
	Female	33 (12)	8 (22)	12 (33)	12 (33)	
Diabetes mellitus (number/percent)		5 (14)	10 (28)	6 (17)	5 (14)	0.36
Hypertension (number/percent)		7 (19)	7 (19)	6 (17)	7 (19)	0.99
Smoking (number/percent)		7 (19)	8 (22)	6 (17)	14 (39)	0.12
Hb level mean(SD)		13.38 (2.03)	13.74 (1.26)	13.28 (1.58)	13.47 (1.82)	0.694
ST-elevation median (IQR)		6.5 (8.8)	8 (8)	7 (6.5)	6.5 (9)	0.303*
EF median (IQR)		35 (15)	30 (19)	35 (14)	35 (14)	0.040*
CK-MB median (IQR)		30.5 (25)	42 (48)	57.5 (93)	51.5 (72)	0.214*
DLVD 0 1 2 3		9 (25) 17 (47.2) 9 (25) 1 (2.8)	2 (5.6) 15 (41.7) 17 (47.2) 2 (5.6)	1 (2.8) 23 (63.9) 12 (33.3) 0 (0)	3 (8.3) 20 (55.6) 11 (30.6) 2 (5.6)	0.044
MR No MR Mild Moderate Severe		5 (13.9) 22 (61.1) 9 (25) 0 (0)	4 (11.1) 21 (58.3) 10 (27.8) 1 (2.8)	9 (25) 15 (41.7) 12 (33.3) 0 (0)	5 (13.9) 18 (50) 10 (27.8) 3 (8.3)	0.304
TIMI 0 1 2		31 (86.1) 5 (13.9) 0 (0)	32 (88.9) 2 (5.6) 2 (5.6)	32 (88.9) 1 (2.8) 3 (8.3)	34 (94.4) 2 (5.6) 0 (0)	0.165

CK-MB, Creatine kinase-muscle/brain; DLVD, Diastolic left ventricular dysfunction; EF, Ejection fraction; Hb, Hemoglobin; MR, Mitral regurgitation; TIMI, Thrombolysis in myocardial infarction

*Based on the Kruskal-Wallis test

Table 2. Comparison of postprocedural quantitative outcomes between the 4 study groups using the analysis of covariance

	Control Group	Intravenous Eptifibatide Group	Intracoronary Eptifibatide Group	Reteplase Group	*P*-value
ST-elevation mean (95% CI)	3.44 (2.67-4.21)	3.48 (2.71-4.25)	2.86 (2.09-3.64)	4.03 (3.26-4.79)	0.22
EF mean (95% CI)	37.02 (35.51-38.53)	38.41 (36.87-39.94)	38.54 (37.04-40.04)	38.81(37.31-40.32)	0.35
CK-MB mean (95% CI)	193.37 (137.8-248.9)	266.7 (211.4-321.9)	209.1 (153.6-264.5)	356.4 (301.0-411.8)	0.0001
Hb mean (95% CI)	12.68 (12.46-12.90)	12.69 (12.47-12.9)	12.86 (12.65-13.08)	12.66 (12.44-12.88)	0.54

EF, Ejection fraction; CK-MB, Creatine kinase-muscle/brain; Hb, Hemoglobin

Table 3. Odds ratios for improving grades of DLVD and MR among the study groups compared with the control group

	DLVD OR* (95% CI)	*P*-value	MR OR** (95% CI)	*P*-value
Control	1	-	1	-
Eptifibatide IV	1.10 (0.38-3.16)	0.86	1.06 (0.40-2.79)	0.90
Eptifibatide IC	0.89 (0.32-2.54)	0.84	0.86 (0.32-2.30)	0.76
Reteplase	0.31 (0.11-0.88)	0.02	0.46 (0.17-1.26)	0.13

DLVD, Diastolic left ventricular dysfunction; IC, Intracoronary; IV, Intravenous; MR, Mitral regurgitation

*Adjusted for the baseline values of DLVD

**adjusted for the baseline values of MR

DISCUSSION

Despite the many benefits of PPCI over fibrinolytic therapy, myocardial perfusion after treatment does not reach the optimum level in all patients.[6] Considering the clinical importance of this issue and the lack of a standard method to prevent this complication, numerous trials have examined different drugs and ways of their administration to improve PPCI outcomes. These studies have used various endpoints to compare the results, but their outcomes are conflicting.[10,12,15,16]

A distinctive feature of our study is the presence of 4 groups (a control group and 3 intervention groups), treated with a glycoprotein IIb/IIIa inhibitor and another drug of fibrinolytic type, as well as the comparison of various drug delivery routes.

The most remarkable result in our study was that none of the 4 groups was different concerning the postprocedural TFG grade as the main endpoint. In recent years, a few studies have compared the use of IV and IC eptifibatide during PPCI with regard to the TFG grade. In a study by Sanati et al,[12] patients with STEMI were randomly assigned to 3 groups: an IV bolus injection followed by a 12-hour infusion, an IC bolus injection followed by an IC infusion, and an IC bolus injection. Chiming in with our study, post-PCI TFG III was not significantly different between the 3 groups. Safi et al[17] also found no difference in TFG after the use of either IV or IC eptifibatide. In an investigation by Namazi et al,[15] patients were randomized into IC abciximab and IV eptifibatide groups. Consistent with the results of our study, they demonstrated that post-PCI TFG III did not differ significantly between the 2 groups. In contrast, Esfandi et al,[16] in their study comparing IV and IC eptifibatide, revealed that TFG after the intervention was better in the IC group.

In the ICE trial,[18] which compared the use of IC and IV eptifibatide, patients undergoing PCI were evaluated for improvements in coronary perfusion by TFG. The results indicated that the IC group was superior to the other group.

Another major finding in our study was that the rise in the CK-MB level from the baseline to 24 hours after PPCI in the reteplase group was more than that in the other 3 groups. The literature offers only 1 study[10] on the comparison between IV and IC tirofiban considering the peak creatine phosphokinase level within 24 hours after PPCI. In contrast with our results, the 2 groups were not different apropos CPK. Also in the study Namazi et al,[15] the enzymatic infarct size assessed by the area under the curve of CK-MB in the first 48 hours after PPCI was similar in the IV eptifibatide and IC abciximab groups.

In the present study, reteplase improved DLVD more than the control group, but the other groups did not differ in this respect. A

study by Pellicori et al[7] is the only investigation to assess DLVD as an endpoint. In their study, 77 candidates for PPCI received either IV or IC abciximab or eptifibatide, followed by an IV infusion of glycoprotein IIb/IIIa inhibitors. There were no significant changes in DLVD 3 days and 1 year after PPCI. Their results are in line with ours insofar as improvements in DLVD were not different between IV and IC glycoprotein IIb/IIIa inhibitors.

We found that the resolution of the ST-segment elevation after PPCI was not different between the 4 study groups. In parallel with our results, Safi et al,[17] in their study comparing IV and IC routes for the use of eptifibatide in PPCI reported no difference concerning ST resolution (from the baseline to 90 minutes after PPCI) between the groups. Likewise, Sanati et al[12] found no difference concerning ST resolution between their 3 study groups of (IV–IV) eptifibatide, (IC–IV) eptifibatide, and IC eptifibatide. In the AIDA-STEMI trial,[19] patients were randomized to receive abciximab as either an IV infusion or directly in blocked coronary arteries. The findings indicated that the IV and IC abciximab groups were not different regarding ST resolution after PPCI. In the trial of CICERO,[20] 534 STEMI patients undergoing PPCI with thrombus aspiration within 12 hours of the onset of symptoms were randomly divided into 2 groups of IC and IV abciximab. In line with our results, there was no difference in ST resolution between the 2 groups. Nonetheless, the use of the IC drug was associated with improved myocardial perfusion, which was assessed by myocardial blush grade and smaller size of the infarct area. On the other hand, the Leipzig trial[21] demonstrated that IC abciximab conferred better ST resolution than IV abciximab. Esfandi et al[16] found that ST resolution was better achieved in the IC eptifibatide group than in the IV eptifibatide group.

Our results identified no significant difference vis-à-vis the postprocedural ejection fraction between the study groups. Safi et al,[17] consistent with our study, found no difference between the IV and IC eptifibatide groups with regard to ejection fraction. In the study by Esfandi et al,[16] comparisons of ejection fraction (5 days after PPCI) showed that, contrary to our study, improvements in ejection fraction after PPCI were more pronounced in the IC group than in the IV group.

In a recently published meta-analysis of 14 trials comparing IV and IC routes for the use of glycoprotein IIb/IIIa inhibitors, the IC group showed superiority regarding postprocedural TFG III, ST resolution, and ejection fraction. [22]

To the best of our knowledge, the present study is the first investigation of its kind to evaluate the use of reteplase in PPCI patients. The use of coronary fibrinolytics in PCI was first studied by Kelly et al,[23] who assigned their study population to PPCI and rescue PCI groups and noted that the use of IC tenecteplase was associated with improved TFG, and it did not increase bleeding. The use of IC reteplase is limited to only a single case report, in which the administration of reteplase during PPCI led to complete coronary blood flow and a long-term favorable outcome in the patient.[24]

The different results of these studies can be due to dissimilar methods of eptifibatide use (a different overall dose and a lack of IV maintenance therapy with eptifibatide), as well as the different characteristics of the patients.

The most likely explanation for the lack of difference in ejection fraction before and after PPCI in our study groups can be justified by the phenomenon of myocardial stunning, which requires time to be resolved. Echocardiography in our study patients was

done 3 to 4 days after PPCI. We, however, believe that it requires at least 2 weeks after PPCI to observe a better recovery in ejection fraction.

We are aware that our research may have limitations. A significant point is that the pain-to-balloon time was not taken into account in our study. The difference in this possible factor between the participants may have affected the observed results. This limitation highlights the difficulty of data collection.

In conclusion, although eptifibatide has shown favorable results in PPCI in some studies, we demonstrated that neither IV nor IC eptifibatide nor reteplase was associated with improvements in coronary blood flow as determined by TFG, ST resolution, and ejection fraction. Further examinations of the results require larger trials.

Acknowledgments

The authors gratefully acknowledge Guilan University of Medical Sciences for its support in implementing the project.

Conflict of Interest

There are no conflicts of interest.

REFERENCES

1. Iversen A, Galatius S, Jensen JS. The optimal route of administration of the glycoprotein IIb/IIIa receptor antagonist abciximab during percutaneous coronary intervention; intravenous versus intracoronary. Curr Cardiol Rev 2008; 4: 293-9. doi: 10.2174/157340308786349480.

2. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. The Lancet 1997; 349: 1498-1504. doi: 10.1016/S0140-6736(96)07492-2

3. Yeh RW, Sidney S, Chandra M, et al. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med 2010; 362: 2155-2165. doi:10.1056/NEJMoa0908610

4. Smilowitz NR, Feit F. The History of primary angioplasty and stenting for acute myocardial infarction. Curr Cardiol Rep 2016; 18: 5. doi: 10.1007/s11886-015-0681-x.

5. Antman EM, Anbe DT, Armstrong PW,et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). J Am Coll Cardiol 2004; 44: 671-719. doi: 10.1161/01.CIR.0000134791.68010.FA

6. Vecchio S, Varani E, Chechi T, et al. Coronary thrombus in patients undergoing primary PCI for STEMI: Prognostic significance and management. World J Cardiol 2014; 6: 381. doi: 10.4330/wjc.v6.i6.381

7. Pellicori P, Torromeo C, Barillà F, et al. Intravenous versus intracoronary bolus of glycoprotein IIb/IIIa inhibitor administration during primary percutaneous coronary intervention on long-term left ventricular systolic and diastolic function. Cardiol J 2013; 20: 310-7. doi: 10.5603/CJ.2013.0077.

8. Henriques J, Zijlstra F, Ottervanger J, et al. Incidence and clinical significance of distal embolization during primary angioplasty for acute myocardial infarction. Eur Heart J 2002; 23: 1112-7. https://doi.org/10.1053/euhj.2001.3035

9. Napodano M, Pasquetto G, Saccà S, et al. Intracoronary thrombectomy improves myocardial reperfusion in patients undergoing direct angioplasty for acute myocardial infarction. J Am Coll Cardiol 2003; 42: 1395-1402. doi: 10.1016/s0735-1097(03)01041-6

10. Erdim R, Erciyes D, Görmez S, et al. Comparison of intracoronary versus intravenous administration of tirofiban in primary percutaneous coronary intervention/Primer perkütan koroner girisim uygulanan hastalarda tirofibanin intrakoroner ve intravenöz bolus dozlarinin

karsilastirilmasi. Anadulu Kardiyoloji Dergisi: AKD 2010; 10: 340. doi: 10.5152/akd.2010.093.

11. Limbruno U, Micheli A, De Carlo M, et al. Mechanical prevention of distal embolization during primary angioplasty: safety, feasibility, and impact on myocardial reperfusion. Circulation 2003; 108(2): 171-6. doi: 10.1161/01.CIR.0000079223.47421.78

12. Sanati HR, Zahedmehr A, Firouzi A, et al. Intracoronary versus Intravenous eptifibatide during percutaneous coronary intervention for acute ST-segment elevation myocardial infarction; a randomized controlled trial. Cardiovasc Interv Ther 2017; 32: 351-7. doi: 10.1007/s12928-016-0418-9

13. Investigators PT. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. N Engl J Med 1998; 339: 436-443. doi: 10.1056/NEJM199808133390704

14. O'gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013; 61: 485-510. doi.org/10.1161/CIR.0b013e3182742c84.

15. Namazi MH, Safi M, Vakili H, et al. Comparison between intracoronary abciximab and intravenous eptifibatide administration during primary percutaneous coronary intervention of acute ST-segment elevation myocardial infarction. J Tehran Heart Cent 2013; 8:132.

16. Esfandi A, Fotouhi M, Allami A, et al. Comparison between the outcomes of intracoronary and intravenous administration of eptifibatide during primary percutaneous coronary intervention in patients with acute ST-elevation myocardial infarction. J Atheroscler Thromb 2016;23:465-476. doi: 10.5551/jat.30965

17. Morteza Safi M, Hosein Vakili M, Habibollah Saadat M, et al. The comparison of intracoronary versus intravenous eptifibatide administration during primary percutaneous coronary intervention of acute ST-segment elevation myocardial infarction. Life Sci J 2012;9.

18. Deibele AJ, Jennings LK, Tcheng JE, et al. Intracoronary eptifibatide bolus administration during percutaneous coronary revascularization for acute coronary syndromes with evaluation of platelet glycoprotein IIb/IIIa receptor occupancy and platelet function: the Intracoronary Eptifibatide (ICE) Trial. Circulation 2010;121:784-791. doi: 10.1161/CIRCULATIONAHA.109.882746

19. Thiele H, Wöhrle J, Neuhaus P, et al. Abciximab Intracoronary versus intravenously Drug Application in ST-Elevation Myocardial Infarction (AIDA STEMI) Investigators Intracoronary compared with intravenous bolus abciximab application during primary percutaneous coronary intervention: design and rationale of the Abciximab Intracoronary versus intravenously Drug Application in ST-Elevation Myocardial Infarction (AIDA STEMI) trial. Am Heart J 2010;159:547-554. DOI: 10.1016/j.ahj.2009.12.038

20. Gu YL, Kampinga MA, Wieringa WG, et al. Intracoronary versus intravenous administration of abciximab in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention with thrombus aspiration: the comparison of intracoronary versus intravenous abciximab administration during emergency reperfusion of ST-segment elevation myocardial infarction (CICERO) trial. Circulation 2010;122:2709-2717. doi: 10.1161/CIRCULATIONAHA.110.002741

21. Thiele H, Schindler K, Friedenberger J, et al. Intracoronary compared with intravenous bolus abciximab application in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: the randomized Leipzig immediate percutaneous coronary intervention abciximab IV versus IC in ST-elevation myocardial infarction trial. Circulation 2008;118:49-57. doi: 10.1161/CIRCULATIONAHA.107.747642

22. Elbadawi A, Elgendy IY, Megaly M, et al. Meta-Analysis of Randomized Trials of Intracoronary Versus Intravenous Glycoprotein IIb/IIIa Inhibitors in Patients With ST-Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. Am J Cardiol 2017;120:1055-1061. DOI: 10.1016/j.amjcard.2017.06.040

23. Kelly RV, Crouch E, Krumnacher H, Cohen MG, et al. Safety of adjunctive intracoronary thrombolytic therapy during complex percutaneous coronary intervention: initial experience with intracoronary tenecteplase. Cathet Cardiovasc interv 2005;66:327-332. DOI: 10.1002/ccd.20521

24. Triantafyllou K, Metaxopoulos P, Babalis D. Primary percutaneous coronary intervention of an unprotected left main using mini-crush drug-eluting stents facilitated by intracoronary reteplase. Cathet Cardiovasc interv 2011;77:515-521. doi: 10.1002/ccd.22815