Original Article

Management of no Reflow during Percutaneous Transcoronary Angioplasty with Catheter-Directed Intracoronary Thrombolysis: A Retrospective Observational Study

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Abstract

Background: Intracoronary thrombus is common in patients with ST-elevation myocardial infarction (STEMI). Percutaneous coronary intervention (PCI) is the treatment of choice for these patients. Intracoronary thrombus is still a challenge during PCI in STEMI, even with dual antiplatelets, glycoprotein IIb/IIIa inhibitor, and anticoagulation. Intracoronary thrombus can cause distal or nonculprit vessel embolization and no-reflow state. No reflow results in large infarct size, adverse left ventricular remodeling, arrhythmias, and death. Recently, catheter-directed intracoronary thrombolysis (ICT) is gaining acceptance in patients with no-reflow due to a large thrombus burden. **Aim:** Evaluation of catheter-directed ICT in patients with acute STEMI who develop no reflow due to large thrombus burden during PCI. **Materials and Methods and Results:** This was a retrospective observational study conducted after approval of the institutional ethics committee in a tertiary care hospital of north India from April 15, 2021 to April 14, 2022, included 1020 adult patients who had undergone coronary evaluation. 37.25% patients had PCI, among these 10% had PCI for acute STEMI. Thrombolysis in myocardial infarction (TIMI) Grade 5 in 79.17% and Grade 4 in 20.83%. ICT was done with low-dose tenecteplase (15 ± 5 mg). The TIMI flow III in 91.67% and II in 8.33% of patients was achieved after intracoronary thrombolysis. Major risk factor was tobacco smoking in 41.67%, and the major complication was left ventricular failure in 33.33%. **Conclusions:** Catheter-directed ICT is safe and effective in reducing thrombus burden, thus improving myocardial reperfusion in STEMI. This condition has a grave prognosis and can lead to adverse cardiac outcomes. There are many drugs that have been tried to manage no reflow. The use of ICT to treat no-reflow state can be life saving with minimal systemic side effects.

Keywords: *Intracoronary thrombolysis, no reflow, percutaneous coronary intervention, ST-elevation myocardial infarction*

Introduction

Acute ST elevation myocardial infarction (STEMI) commonly occurs as a result of thrombosis of a disrupted atherosclerotic plaque, that lead to complete occlusion of a major coronary artery. Thrombus is seen in 91.6% of patients with STEMI on coronary angiography.[1] 16.4% of patients with acute coronary syndrome show a large coronary thrombus load.[2] Primary percutaneous coronary intervention (PCI) is the preferred treatment for acute STEMI, but it can be associated with a large intracoronary thrombus load in 70% of patients.[3] This can lead to larger infarct size, distal embolization, no-reflow state, and increased risk of stent thrombosis. The risk factors for no reflow include diabetes, hypertension, smoking, and dyslipidemia. This increases the mortality rate and major adverse cardiac events (MACE), like poor healing of the infarct, adverse remodeling, arrhythmias, and left ventricular failure.[4-7] The cause of injury include ischemia, reperfusion, endothelial dysfunction, microvascular spasm, and distal thromboembolism.[8,9] The risk factors for massive coronary thrombosis are hypercoagulability, hypercholesterolemia, hyperhomocysteinemia, hyperglycemia, leukocytosis, smoking, cocaine and methamphetamine, vasculitis, male sex, slow coronary flow, right coronary artery, late presentation >12 h, angry clot phenomenon, cardiogenic shock, failed thrombolysis and inadequate dual antiplatelets.[10] Large number of

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interventions has been used like intracoronary vasodilators therapy, including nitroprusside, nicardipine, nitroglycerine, adrenaline, adenosine or verapamil, thrombectomy and aspiration, distal protection devices and intracoronary glycoprotein (Gp) IIb/IIIa inhibitors for treatment of no reflow. Intracoronary delivery of thrombolytic agent results in higher concentration at the desired site and better thrombolysis in STEMI with massive thrombus load and improved myocardial reperfusion without risk of major bleeding.[11] delivery of thrombolytics before thrombectomy in patients with STEMI undergoing primary PCI (DISSOLUTION) trial showed better reperfusion and clinical outcome.[12] Catheter-directed intracoronary thrombolysis (ICT) has been used in patients with failure of thrombus aspiration (TA),[13-15] large ectatic vessels,[16] and adjunctive therapy to PCI in poor reperfusion.[17] Recently, some studies have shown favorable results with fibrinolytic therapy during PCI.[17] This article is about using ICT with tenecteplase for successful management of no reflow during primary PCI in STEMI and total coronary occlusion.

Materials and Methods

This was a retrospective observational study conducted after approval from the institutional ethics committee (Reference no. AU/EC_BHR/2K22/164) in the Cardiac Care Unit of Adesh Institute of Medical Sciences and Research Bathinda from April 15, 2021 to April 14, 2022. The study included adult patients of both sexes, who had undergone coronary evaluation, percutaneous transcoronary angioplasty (PTCA) for STEMI, developed no reflow state (TIMI 0 flow), and required ICT with tenectaplase. The exclusion criteria included patients with coronary dissection or spasms, bleeding disorders, allergic to thrombolytic agents, and contraindications to thrombolytic agents.

The data on age, sex, diagnosis, any addiction, comorbid conditions, no-reflow state, ICT, complications and dose of the thrombolytic agent were recorded.

The quantification of thrombus load was defined by thrombolysis in myocardial infarction (TIMI) grading was as follows.[10]

- No thrombus on angiography
- Decreased contrast density, the irregular contour of the lesion, and smooth convex meniscus at the total occlusive site suggest the possibility of thrombus
- Marked irregular contour of the lesion with a filling defect the largest dimension of thrombus is less than half the diameter of the artery in multiple views on angiography, is confirmatory of thrombus
- Greater than half to <2 artery diameters in multiple views on angiography suggest a definite presence of thrombus
- Definite large size thrombus present with largest dimension >2 vessel diameters, suggest the definite presence of a large thrombus
- Complete occlusion of the artery.

TIMI flow grading was defined as follows.[18]

- No penetration of contrast in infarct-related vessel
- Penetration of some contrast beyond the obstruction but no perfusion in the distal coronaries
- Perfusion in whole infarct-related vessel, but with delayed flow
- Full perfusion of infarct-related vessel and normal flow.

Statistical analysis

The data were collected, tabulated and qualitatively analyzed and expressed as a frequency distribution of percentages.

Results

Patient characteristics such as age, sex, locality, and risk factors are shown in Table 1. Total 1020 (male – 710, female-310) patients had undergone coronary evaluation, 380 (37.25%) patients had PTCA. Among these, 102 (10%) patients had undergone PTCA for acute STEMI. 32 (males – 24, females – 08) patients developed no-reflow state, (24 [75%] due to high thrombus load, 6 [18.75%] coronary spasms and 2 [6.25%] coronary dissection). Smoking of tobacco was seen in 41.67%, diabetes in 37.5%, family history in 20.83%, and dyslipidemia in 8.33% of patients. The diagnosis, coronary intervention, no-reflow state, Grade of thrombus, dose of tenectaplase, flow achieved, and complications seen are shown in Table 2. TIMI flow Grade III was achieved in 91.67% patients with ICT and Grade II in 8.33% of patients [Table 2]. Patients with coronary spasms and dissection were excluded from the study.

Discussion

Currently, primary PCI is the treatment of choice for STEMI.[3] Primary PCI is better than thrombolysis for the patency of the artery. This resulted in smaller infarcts and decreased complications like recurrent myocardial infarction and death. Management of large thrombus load during primary PCI is challenging.

Table 1: Patient characteristics who developed no reflow with large thrombus burden

Variable	Sex		Total (*n*)
	Male, *n* (%)	Female, *n* (%)	
Age (years), mean±SD	54±14	50±12	
Risk factor			
Tobacco smoking	10 (41.67)	-	10 (41.67)
Family history	3 (12.5)	2 (8.33)	5 (20.83)
Diabetes	6 (25)	3 (12.5)	9 (37.5)
Dyslipidemia	2 (8.33)	-	2 (8.33)
Locality			
Urban	8 (33.33)	5 (20.83)	13 (54.16)
Rural	7 (29.17)	4 (16.67)	11 (45.84)

SD: Standard deviation

Table 2: Clinical diagnosis and complications

Sex	Male, *n* (%)	Female, *n* (%)	Total, *n* (%)	
Diagnosis				
SVD	428 (41.96)	208 (20.39)	636 (62.35)	1020 (100)
DVD	210 (20.59)	76 (7.45)	286 (28.04)	
TVD	72 (7.06)	26 (2.55)	98 (9.61)	
Percutaneous coronary intervention				
NSTEMI	212 (20.78)	66 (6.47)	278 (27.25)	380 (37.25)
STEMI	70 (6.86)	32 (3.14)	102 (10)	
No reflow				
Thrombus	18 (56.25)	6 (18.75)	24 (75)	32 (100)
Dissection	2 (6.25)	-	2 (6.25)	
Spasm	4 (12.50)	2 (6.25)	6 (18.75)	
TIMI grade of thrombus				
5	16 (66.67)	3 (12.5)	19 (79.17)	
4	2 (8.33)	3 (12.5)	5 (20.83)	
Dose of tenectaplase (mg), mean±SD	15±5	15±5		
TIMI flow achieved				
III	17 (70.84)	5 (20.83)	22 (91.67)	24 (100)
II	1 (4.17)	1 (4.17)	2 (8.33)	
Complications in patients with intracoronary tenectaplase				
LVF	6 (25)	2 (8.33)	8 (33.33)	
VT	3 (12.5)	-	3 (12.5)	
Mortality	1 (4.17)	-	1 (4.17)	
Minor bleeding	1 (4.17)	1 (4.17)	2 (8.33)	

TIMI: Thrombolysis in myocardial infarction; SVD: Single-vessel disease; DVD: Double-vessel disease; TVD: Tripple-vessel disease; LVF: Left ventricular failure; VT: Ventricular tachycardia; SD: Standard deviation; STEMI: ST-elevation myocardial infarction; NSTEMI: Non-STEMI

The target of intervention is not only to open the epicardial artery but also to achieve normal myocardial blood flow. The no-reflow state can occur with any method of revascularization but is commonly seen during PTCA. The knowledge of risk factors that can lead to no-reflow state before PCI can help in the prevention of this condition. The preventive strategies include primary stenting, avoidance of high-pressure stent deployment, and thrombectomy before the intervention.

The no-reflow state can be seen after ballooning or stenting a lesion. This can be due to microvasculature obstruction, incomplete dilatation of lesion, coronary spasm, or dissection with or without *in situ* thrombosis. After the procedure, there should be TIMI III coronary flow, low TIMI frame count, and normal myocardial blush Grade.[18,19] The no-reflow may be seen in 5%–60%.[20] It is commonly seen in degenerated vein grafts and with the use of rotational atherectomy devices. The patient-related factors associated with high risk of no-reflow include late presentation to the catheterization laboratory, hyperglycemia, and hypercholesterolemia.[21] Rezkalla *et al*.[21] reported no reflow in 32% of cases undergoing PCI for STEMI. No reflow was defined as TIMI less than Grade III and as myocardial blushing Grade less than III.

In this study, no reflow was seen in 31.37% of patients who had PCI for STEMI. The low dose of intracoronary tenecteplase was effective in treating high thrombus burden and achieved TIMI flow Grade III in 91.67% and Grade II in 8.33%. The large thrombus burden was seen in patients with tobacco smoking, followed by diabetes, family history, and dyslipidemia, respectively. Major complications seen were Left ventricular failure in 33.33%, Ventricular Tachycardia in 12.5%, minor bleeding in 8.33% and mortality in 4.17%.

Intracoronary administration of thrombolytic agent results in a higher concentration of thrombolytics at the local site and better thrombolysis. Small studies of intracoronary administration of thrombolytic agent as adjunctive therapy to primary PCI have shown better myocardial reperfusion and reduced thrombus burden without any major risk of bleeding in patients with STEMI with massive thrombus load and failed manual aspiration.[10]

When the state of no reflow occurs during PCI, the primary aim should be the optimal treatment of infarct-related artery and the optimal use of available options. Despite recent remarkable research on this topic, no evidence-based standard treatment is available at present.

Patients with no reflow, who were treated with intracoronary vasodilators such as adenosine, nitroprusside, nicardipine, adrenaline, or verapamil had better coronary flow and prognosis. The choice of intracoronary vasodilator

does not matter, but the aim should be to treat no reflow as soon as possible.[21] Adenosine 100–200 μg,[22] nicardipine of 400 μg,[23] or nitroprusside 50–300 μg,[24] are commonly used. The optimal control of blood sugar before the procedure can decrease the incidence of no reflow,[25] by indirect effect via improving the coronary microvascular circulation[26] and direct via the effects of acute hyperglycemia on reperfusion injury.[27]

Many pharmacological and mechanical approaches have been tried to reduce thrombus load. Early treatment with dual antiplatelets reduces thrombus load and improves clinical outcomes. Aspirin is given 325 mg as a loading dose orally along with a loading dose of clopidogrel, prasugrel, and ticagrelor.

Intracoronary administration of abciximab in the affected vessel provides higher local concentration, higher receptor occupancy, and a higher rate of thrombus resolution.[28] A meta-analysis by Shimada *et al*. reported better TIMI flow in the affected vessel and short-term mortality without any risk of increased bleeding with intracoronary bolus of GPI during PCI.[29] However, its role needs large randomized trials.

DISSOLUTION trial, a randomized trial of ICT[11] included 102 patients of STEMI and a large thrombus load in infarct-related artery. They were randomly given either intracoronary bolus of urokinase (n = 51) or normal saline (n = 51) through a microcatheter, followed by manual aspiration of thrombus. The intracoronary urokinase achieved a significantly higher incidence of TIMI Grade III flow, higher Grade of myocardial blush, more resolution of ST segment and reduced TIMI frame count. A recent trial by McCartney *et al*.[30] included 440 cases of STEMI, who presented with symptoms of <6 h duration, received low dose of intracoronary alteplase (10 mg or 20 mg) adjunctive to primary PCI, the trial has not shown any reduction in microvascular obstruction or MACE (cardiac death, nonfatal MI, unplanned hospitalization for heart failure).[31] Present, no significant data are available in support for use of intracoronary fibrinolytic.

Currently, two trials, including Adjunctive Low-dose Intracoronary Recombinant Tissue Plasminogen Activator Versus Placebo for Primary PCI in Patients with STEMI and A Randomised Trial to Evaluate the Efficacy of Low-dose Intracoronary Tenecteplase in STEMI Patients With High Microvascular Resistance (RESTORE-MI) Post PCI are in PHASE 3, and can address some issues.

Other treatment options include thrombectomy devices, embolic protection devices, manual TA, mechanical thrombectomy devices, excimer laser coronary atherectomy, distal occlusion aspiration devices, distal embolic filters, proximal occlusion aspiration devices, direct stenting, but none of them is recommended currently due to paucity of available data.[31]

Limitation

This is a retrospective study in a small sample size, and a bigger prospective study is needed to demonstrate the benefits of ICT with tenecteplase to treat no-reflow state.

Conclusions

Coronary no reflow is a serious condition during PTCA in patients with STEMI. Normal coronary flow is essential to get the maximal benefit of angioplasty. No reflow can lead to major cardiac adverse events such as bigger infarct size, acute left ventricular failure, ventricular arrhythmias, and increased mortality. Various agents such as adenosine, nitroglycerine, Gp IIb/IIIa inhibitors have been used to treat no-reflow state. The use of ICT to treat no-reflow state can be life saving with minimal systemic side effects. Short door to balloon time, avoiding long stents, and avoiding high pressure during stent placement may be helpful in avoiding this condition. A standard operating procedure may be helpful to prevent and treat this dreadful condition and its complications.

Ethical statement

The study was approved by the institutional ethics committee of Adesh Institute of Medical Sciences and Research, Batinda Ref no.AU/EC_BHR/2K22/164 dated 19th May 2022.

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Conflicts of interest

There are no conflicts of interest.

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