PREDICTORS OF CORONARY SLOW FLOW OR NO REFLOW PHENOMENA AFTER PRIMARY PERCUTANEOUS CORONARY INTERVENTION

Ajay Sharma[1], Tarun Kumar[2], Ankit Gupta[3], Bhagya Narayan Pandit[4]

[1]Consultant, Department of Cardiology, PGIMER, Dr. Ram Manohar Lohiya Hospital, Delhi, India.
[2]Associate Professor, Department of Cardiology, PGIMER, Dr. Ram Manohar Lohiya Hospital, Delhi, India.
[3]Third Year DM Resident, Department Cardiology, PGIMER, Dr. Ram Manohar Lohiya Hospital, Delhi, India.
[4]Associate Professor, Department of Cardiology, PGIMER, Dr. Ram Manohar Lohiya Hospital, Delhi, India.

ABSTRACT

BACKGROUND

The treatment of acute myocardial infarction (AMI) is thought to restore antegrade blood flow in the infarct-related artery with percutaneous coronary interventions (PCI). The present study was undertaken to identify the clinical factors, biochemical markers, angiographic findings and procedural features which predict the coronary slow flow/no reflow phenomenon in patients with AMI after primary PCI.

METHODS

A total of 150 patients between 18 to 75 years of age with first episode of AMI undergoing primary PCI were enrolled from January 2015 to June 2016. According to thrombolysis in myocardial infarction (TIMI), patients were divided into normal flow group and slow/no reflow group. The result of primary angioplasty was confirmed on the basis of TIMI flow grade, myocardial blush score and TIMI thrombus grade. Chi-square test was used to analyse categorical variables. Student's t-test and analysis of variance were used for continuous variables. Multivariate analysis was performed to identify independent predictors of no-reflow phenomenon.

RESULTS

Out of 150 patients, 30 (20%) patients developed slowly flow/no reflow after primary PCI. Multivariate analysis showed random blood sugar (p value= 0.031), C-reactive protein (p value= 0.020), higher thrombus grade (p value= 0.07) and length of the stents used (p value= 0.017) were the independent predictors of slow flow/no reflow.

CONCLUSIONS

The occurrence of slow/no reflow after primary PCI for acute myocardial infarction can be predicted by clinical, biochemical, angiographic and procedural features.

KEYWORDS

Acute Myocardial Infarction, No-Reflow Phenomenon, Percutaneous Coronary Intervention

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BACKGROUND

Coronary artery disease (CAD) is the foremost cause of disability and death in the world and is one of the top five causes of death in India.[1] One of the serious complications of CAD is ST-elevation myocardial infarction (STEMI), a life threatening medical emergency that results from a sudden, occlusive thrombus in the coronary artery. When STEMI patients treated promptly with reperfusion therapy, significant reduction in mortality and morbidity has been observed.[2] Since the introduction of percutaneous coronary intervention (PCI) in 1978,[3] fibrinolytic therapy has been replaced by PCI as the chosen reperfusion strategy in STEMI patients, with better angiographic reperfusion rates at 90 minutes than those achieved with pharmacological reperfusion.[4] However, a significant percentage of patients do not achieve adequate micro vascular reperfusion despite the restoration of epicardial flow in the treated vessel. This is called as coronary slow flow phenomenon. In no-reflow phenomenon, primary coronary interventions for acute myocardial infarction (AMI) is the absence of myocardial perfusion restitution after adequate recanalization of the infarct-related artery.[5] The incidence of slow flow or no-reflow phenomenon is present in 10% to 54% of the procedures depending on the characteristics of the population studied and on the methods used for its diagnosis. It is associated with an adverse clinical outcome with greater short and long term progression to heart failure and increased mortality.[6-10] This unique phenomenon is still poorly understood. The present study was undertaken to identify clinical factors, biochemical markers, angiographic

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Corresponding Author:
Dr. Tarun Kumar,
Associate Professor,
Department of Cardiology,
PGIMER, Dr. Ram Manohar Lohiya Hospital,
Delhi, India.
E-mail: drtarunk77@yahoo.co.in
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findings and procedural features which could predict the coronary slow flow/no reflow phenomenon in patients with AMI after primary PCI.

METHODS

Study Design

This was a prospective, observational study conducted from January 2015 to June 2016. Consecutive patients who underwent primary PCI with stenting were included in this study. Patients who did not receive stent implantation were excluded from the study. A written consent form was received from each patient enrolled in the study and the study protocol was approved by the Institutional Ethics Committee of the hospital.

Data Collection

Patients were evaluated for-

1. Clinical parameters like age, gender, hypertension, diabetes mellitus, smoking, family history of CAD, previous myocardial infarction, Killip class, duration of symptoms, infarct territory and door to balloon time.
2. Biochemical parameters like renal function tests, random blood sugar, total leucocyte count, neutrophil lymphocyte ratio, c-reactive protein and creatinine levels.
3. Procedural and angiographic parameters like multi vessel disease, arteries involved, lesion length, thrombus burden, and number of stents implanted, glycoprotein IIb/IIIa inhibitors and aspiration thrombectomy usage.

Outcome Measures

The results of primary angioplasty were confirmed on the basis of thrombolysis in myocardial infarction (TIMI) flow grade and TIMI thrombus grade. Various clinical, biochemical and procedural and angiographic parameters were compared in patients with normal flow vs. slow flow/no reflow. Here, no-flow was defined as the cessation of flow into distal coronary artery in the absence of a clear angiographic explanation of impaired flow (dissection, thrombus). Slow-flow was defined as the diminution of coronary flow by 1–2 TIMI grades from the baseline ante grade flow in the absence of an epicardial obstruction.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation and categorical variables were presented as count and percentage. The Chi-square test was used to analyse categorical variables. Student's t-test was used for continuous variables. Multivariate analyses were performed to identify independent predictors of no-reflow phenomenon. Statistical analysis was made using SPSS. A p-value <0.05 was considered statistically significant.

RESULTS

This study included 165 consecutive patients who were taken for primary PCI between January 2015 and June 2016. Fifteen patients were excluded from this study because no stents were deployed. Finally, a total of 150 patients were included for further evaluation. The baseline characteristics of all patients included in the study is shown in

Demographic Characteristics	Patients (N= 150)
Age (mean ± SD, years)	59.3 ± 13.0
Male, n (%)	87 (58.0%)
Clinical Characteristics	
Time of presentation (mean ± SD, hour after symptom onset)	7.3 ± 3.3
Pulse (mean ± SD, per min)	75.9 ± 18.7
SBP (mean ± SD, mmHg)	124.6 ± 24.8
Door to balloon time (mean ± SD, min)	63.0 ± 29.7
Risk Factors	
Smoking, n (%)	78 (52.0%)
Diabetes, n (%)	45 (30.0%)
Hypertension, n (%)	57 (38.0%)
Family history, n (%)	12 (8.0%)
Past history, n (%)	21 (14.0%)
Killip Class	
Class I, n (%)	78 (52.0%)
Class II, n (%)	42 (28.0%)
Class III, n (%)	24 (16.0%)
Class IV, n (%)	6 (4.0%)
Biochemical Parameters	
TLC (mean ± SD, cells / mm^3)	11177.1 ± 2978.0
Platelet count (mean ± SD, lakh / mm^3)	3.1 ± 1.2
Creatinine (mean ± SD, mg/dl)	1.0 ± 0.4
RBS (mean ± SD, mg/dl)	155.8 ± 38.5

Table 1. Baseline Characteristics of Patients

SD: Standard deviation; SBP: Systolic blood pressure; TLC: Total leucocyte count; RBS: Random blood sugar

Characteristics	Normal Flow (n= 120)	Slow Flow/no Reflow (n= 30)	p Value
Age (mean ± SD, years)	57.8 ± 13.7	64.8± 7.5	<0.009
Male, n (%)	69 (57.5%)	18 (60.0%)	0.84
Pulse (mean ± SD, per min)	74.6 ± 17.4	80.9 ± 22.9	0.167
SBP (mean ± SD, mmHg)	126.1 ± 24.9	119.0 ± 24.5	0.163
Smoker, n (%)	60 (50.0%)	18 (60.0%)	0.346
Diabetes mellitus, n (%)	36(30.0%)	9 (30.0%)	0.99
Hypertension, n (%)	45(37.5%)	12 (40.0%)	0.492
Previous CAD, n (%)	18 (15.0%)	3 (10.0%)	0.48
Killip class-I, n (%)	72 (60.0%)	6 (20.0%)	0.07
Killip class-II, n (%)	33 (27.5%)	9 (30.0%)	0.82
Killip class-III, n (%)	15 (12.5%)	9 (30.0%)	0.02
Killip class-IV, n (%)	0 (0.0%)	6 (20.0%)	<0.001
TLC (mean ± SD, cells/ mm^3)	11640.0 ± 3009.0	11061.0 ± 2972.4	0.346
RBS (mean ± SD, mg/dl)	148.9 ± 34.5	183.6 ± 41.7	0.031
Creatinine (mean ± SD, mg/dl)	1.0 ± 0.4	0.9 ± 0.3	0.074
Platelet count (mean ± SD, lakh/mm^3)	3.0 ± 1.2	3.3 ± 1.5	0.1002
N/L ratio (mean ± SD)	6.9 ± 1.6	7.7 ± 2.1	0.028
CPKMB (mean ± SD, ng/ml)	163.1 ± 76.48	196.6 ± 77.6	0.034
C-reactive protein, n (%)	51(42.5%)	19(63.3%)	0.020
Anterior wall myocardial infarction, n (%)	60 (50.0%)	15 (50.0%)	0.99
Inferior wall myocardial infarction, n (%)	48 (40.0%)	12 (40.0%)	0.99
Lateral wall myocardial infarction, n (%)	9 (7.5%)	0 (0.0%)	0.131
Posterior wall myocardial infarction, n (%)	3 (2.5%)	3 (10.0%)	0.233

Table 2. Clinical Characteristics

SD: Standard deviation; SBP: Systolic blood pressure; TLC: Total leucocyte count; RBS: Random blood sugar; N/L: Neutrophil lymphocyte; CPKMB: Creatine kinase-muscle/brain; CAD: Coronary artery disease; NS: Not significant

Characteristics		Normal Flow (n= 120)	Slow Flow/no Reflow (n= 30)	p Value
Thrombus Grade, n (%)	Mild	60 (50%)	9 (30%)	0.06
	Moderate	33 (27.5%)	6 (20%)	0.48
	Severe	27 (22.5%)	15 (50%)	0.005
Door-Balloon time (mean ± SD, min)		61.25 ± 28.1	74.0 ± 33.4	0.0341
Aspiration thrombectomy, n (%)	Yes	57 (47.5%)	15 (50%)	0.806
	No	63 (52.5%)	15 (50%)	
Culprit artery, n (%)	LAD	66 (55%)	15 (50%)	0.68
	RCA	30 (25%)	9 (30%)	0.64
	LCx / OM	24 (20%)	6 (20%)	1.0
Location, n (%)	Proximal	51 (42.5%)	9 (30%)	0.29
	Mid	60(50%)	18 (60%)	0.414
	Distal	9 (7.5%)	3 (10%)	0.70
Stent (mean ± SD, mm)	Length	28.58	32.9	0.017
	Diameter	2.9	2.9	0.99

Table 3. Procedural Characteristics

SD: standard deviation; LAD: left anterior descending artery; RCA: right coronary artery; LCx: left circumflex; OM: obtuse marginal

Out of 150 patients 78 patients (52.0%) were in Killip class I, 42 patients (28.0%) were in Killip class II, 24 patients (16.0%) were in Killip class III and 6 patients (4.0%) were in Killip class IV at the time of presentation. Electrocardiogram revealed that 75 patients (50.0%) had anterior wall myocardial infarction, 60 (40.0%) had Inferior wall myocardial infarction, 9 patients (6.0%) had lateral wall myocardial infarction and 6 patients (4.0%) had posterior wall myocardial infarction. Coronary angiogram showed left anterior descending as the culprit vessel in 81 (54.0%) patients, right coronary artery as culprit vessel in 39 (26.0%) patients and left circumflex/obtuse marginal as culprit vessel in 30 (20.0%) patients. Sixty-nine (46.0%) patients had thrombus of mild grade, 39 (26.0%) patients had moderate severity and 42 (28.0%) patients had severe grade thrombus in the culprit vessels. Of 150 patients, 30 (20.0%) patients developed slowly flow/no reflow. Mean age of the patient in the slow flow/no reflow group was 64.8 ± 7.5 years and 57.8 ± 13.7 years in normal flow group (p-value of < 0.009). Total of 69 patients (57.5%) in the normal flow group were male and 18 patients (60.0%) in slow flow/no reflow group were males. Out of 120 patients in the normal flow group, 15 patients (12.5%) presented within 0-3 hours, 42 patients (35.0%) within 3-6 hours, 33 patients (27.5%) within 6-9 hours, 21 patients (17.5%) within 9-12 hours and 9 (7.5%) patients presented after 12 hours of symptom onset. Out of 30 patients in the slow flow/no reflow group, 0 patient (0.0%) presented within 0-3 hours of symptom onset, 6 patients (20.0%) presented within 3-6 hours, 9 patients (30.0%) presented within 6-9 hours, 12 patients (40.0%) presented within 9-12 hours and 3 patients (10.0%) presented after 12 hours. Clinical and procedural characteristics of normal flow versus patients with slow flow/no reflow group were compared in (Table 1)

Multivariate analysis showed random blood sugar (p value= 0.031), C-reactive protein (p value= 0.020), higher thrombus grade (p value= 0.07) and length of the stent used (p value= 0.017) as the independent predictors of slow flow/no reflow.

DISCUSSION

In this study, 150 patients with AMI were enrolled who underwent primary PCI. The rate of slow flow/no reflow phenomenon after primary PCI was 20% in present study, which is similar to previously reported literature (5%–25%).[11] The cause of no-reflow after primary PCI in patients with STEMI is multifactorial. The possible mechanisms of no-reflow include endothelial dysfunction, micro vascular disorders, vasospasm, distal micro-embolization and reperfusion injury. In present study, a significant difference was observed between age and TIMI flow. The mean age of the patient in the slow flow/no reflow group was 64.8 ± 7.5 years and in normal flow group was 57.8 ± 13.7 years (p <0.009). Iwakura et al[9] also showed a significant correlation between age and TIMI flow in their study of 146 patients (p= 0.003). Majority of the patient in our study, presented within 3–6 hours of symptoms and the mean time of presentation in normal and slow flow/no reflow group was 6.9 ± 3.3 hours and 8.7 ± 2.9 hours, respectively. There was statistically significant difference with mean time of presentation and slow flow/no reflow in patients presenting within 9-12 hours of symptom onset (p= 0.012). Ndrepepa et al[6] in their study of 1140 patients also found that delay in treatment from the onset of symptoms leads to more slow flow/no reflow after primary PCI (p= 0.001). In present study, it was observed that in patients with higher Killip class have more chances of slow flow/no reflow after primary PCI. AMI patients with Killip class ≥3 at admission are frequently accompanied by severely impaired left ventricular function. Previous studies have also shown that higher Killip class due to large area of impaired myocardium is associated with final TIMI flow <3.[12-14] Thus, it is reasonable to propose that Killip class ≥3 at admission with lower left ventricular ejection fraction, which might be attributed to large area of infarction, could have large micro vascular bed injury, increased left ventricular end-diastolic pressure, and decreased coronary perfusion pressure, leading to resultant non optimal coronary flow.

In the present study, we found that angiographic slow flow/no reflow occurred more frequently in patients with acute hyperglycaemia on admission (RBS: 183.6 ± 41.7 vs 148.9 ± 34.5 mg/dl, p= 0.031). Several mechanisms could explain the association between hyperglycaemia and angiographic slow flow/no reflow. Acute hyperglycaemia aggravates platelet dependent thrombus formation,[15] attenuates endothelium dependent vasodilatation,[16] and reduces collateral blood flow by adversely affecting nitric oxide availability.[17] These changes are associated with impairment in micro vascular function before reperfusion and are related to angiographic slow flow/no reflow. Significant difference was found between neutrophil/lymphocyte (N/L) ratio (6.9 ± 1.6 vs. 7.7 ± 2.1, p= 0.028) and final TIMI flow in our study which suggested a difference between the inflammatory response and leukocyte occlusions of coronary vascular bed. Akpek et al[18] reported that N/L ratio and C-reactive protein had a significant and positive correlation with no-reflow in STEMI patients treated with PCI. In the literature, clinical value of

N/L ratio was evaluated not only in no-reflow phenomenon but also in different STEMI patient groups. Sahin et al[19] found that N/L ratio of STEMI patients with a high Syntax score (>18) was also higher in comparison to N/L ratio of patients with a relatively lower Syntax score (<11) (6.5 ± 3.9 vs. 4.0 ± 2.9). In our study, CRP levels in the patient group with slow flow/no reflow were higher than those with normal coronary flow, and the difference was statistically significant. Our study shows that longer length of the stent used in primary PCI increases the chances of slow flow/no reflow with p value of 0.017. The longer the target lesion, the larger amount of thrombus and plaque burden. This would explain the high risk for slow flow/no reflow observed in these patients after primary PCI.[20,21]

Limitations

The number of patients included in the study were small. Patients were not followed up to see clinical outcomes. Myocardial contrast echocardiography, ST-segment resolution, and angiographic "blushing" scores may provide a more meaningful assessment of reperfusion efficacy than the TIMI flow grade.

CONCLUSIONS

The incidence of slow flow/no reflow after primary PCI is 20% and higher age, higher Killip class at presentation, more delay in time of presentation, higher random blood sugar, lower N/L ratio, C-reactive protein, higher grade of thrombus and longer stent used are the predictive factors for slow flow/no reflow phenomena after primary PCI. However, RBS, CRP, higher thrombus grade and longer length of stent used were the independent predictors of slow flow/ no reflow after primary PCI.

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