Treatment of Refractory No-Reflow in Cardiac Catheterization Laboratory; Role of Intracoronary Verapamil (A Case Report)

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ABSTRACT

The no reflow phenomenon is a feared complication in Percutaneous Coronary Intervention (PCI) procedures including elective as well as primary PCI (Percutaneous Coronary Intervention), and results in worse prognosis. A number of etiological factors are involved in pathogenesis of no reflow phenomenon. These include distal athero embolization, ischemic and reperfusion injury, microvascular spasm and endothelial dysfunction. The treatment of no reflow depends on underlying mechanism and includes pharmacological as well as non-pharmacological interventions. Pharmacological agents include vasodilators like adenosine, sodium nitroprusside, verapamil, in addition to adrenaline (intracoronary) and, GpIIa/IIIb inhibitors. Non pharmacological measures include mechanical thrombus aspiration. Among pharmacological agents, Verapamil is usually the least preferred agent because of its negative ionotropic effect. Here, we describe a case of refractory no reflow in a patient undergoing primary PCI to right coronary artery (RCA), which was treated with a no. of pharmacological agents as well as aspiration thrombectomy but without much success and finally responded to intracoronary verapamil.

Keywords: Acute coronary syndrome (ACS), Athero embolization, Endothelial dysfunction, Lack of myocardial perfusion, Microvascular spasm, Myocardial infarction (MI), No reflow, Percutaneous coronary intervention (PCI), Reperfusion injury, Vasodilators.

INTRODUCTION

The no reflow phenomenon is traditionally defined as absence of myocardial perfusion despite flow restoration in the occluded epicardial coronary artery. The underlying pathological factors include ischemic and reperfusion injury, distal thromboembolism, endothelial dysfunction and microvascular spasm.[1] Treatment is directed as per etiology of no reflow phenomenon and includes vasodilators, antiplatelet agents and mechanical thrombus aspiration. Untreated no- reflow leads to worse outcomes.[2]

CASE REPORT

An 89 years old hypertensive lady, with no previous history of ischemic heart disease, presented to emergency department with central chest pain for 6 hours. Her blood pressure on arrival was 190/95, heart rate; 65/min, respiratory rate, 20/min. Her respiratory and cardiovascular examination did not reveal any abnormality. Electrocardiogram (ECG) was done in emergency and it revealed acute inferoposterior myocardial infarction and patient was taken to Cardiac Cath Lab for primary PCI, after taking informed

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consent. Angiogram showed critical disease in mid-course of left anterior descending artery (LAD) and 100% occlusion of proximal left circumflex (LCX) artery, which was also being cross filled via LAD. The right coronary artery (RCA) was the likely culprit and was occluded with thrombus in proximal course (Figure-1).

Figure-1: Culprit Lesion Image

Primary PCI was performed on the RCA using run through guide wire. The lesion was pre dilated with 2.0 x 15mm balloon and stenting with 3.0 x 48mm DES and TIMI III flow was achieved (Figure-2).

Figure-2: Pre Dilatation RCA

Figure-IV: No- Reflow

Post dilation was done with 3.25 x 15mm NC balloon and final contrast injection showed, "no-reflow phenomenon" (Figure-3).

Figure-3: Post Dilatation RCA

Figure-V: TIMI-III Flow

Patient's blood pressure dropped and she was started on ionotropic support and temporary pace-maker was placed. She was treated with multiple boluses of 100 microgram intracoronary adenosine upto 1000 microgram, intracoronary tirofiban 50 microgram boluses upto 100 microgram, intracoronary nitrates 100 microgram bolus upto 1000 microgram and intra-coronary adrenaline 100 microgram. The abovementioned drugs were given 1st via guiding catheter and then via micro catheter in distal vessel but thrombolysis in myocardial infarction (TIMI) grade did not improve (Figure-4). Thrombuster was used for thrombus aspiration in distal circulation but the aspirate did not reveal any thrombus. Finally, intracoronary verapamil was given in 200 microgram bolus after which the contrast injection showed TIMI-III flow (figure-5). Patient was shifted to CCU afterwards where her ionotropic support was gradually tapered off. She remained stable and pain free and was discharged after two days.

DISCUSSION

No reflow phenomenon is a well-known complication of primary percutaneous intervention (PCI). The incidence of no reflow in primary percutaneous intervention (PCI) is around 10% and it results in higher mortality at 30 days, if left untreated (32% vs. 2.8%, $p < 0.001$).[2] It is characterized by sudden loss of epicardial flow, after ballooning or stenting a lesion. The first step is to do an intravascular ultra-sound (IVUS) to differentiate between spasm, dissection and distinguish them from microvascular dysfunction. Current pharmacological treatment mainly consists of vasodilator therapy, local antiplatelet therapy along with intracoronary adrenaline and non-pharmacological measures like mechanical thrombus aspiration.

Among the pharmacological agents intracoronary vasodilators (adenosine, nitroprusside and verapamil) have Class-IIa recommendation in 2011 ACC guidelines for PCI and local antiplatelets like eptifibatide and tirofiban receive a Class-IIa recommendation for bailout in treatment of no re-flow, as per 2018 ESC Myocardial revascularization guidelines.[3]

Adenosine: Is a purine analog and has a well-known role in treatment of no reflow. It increases microvascular flow by vasodilation, inhibits platelets, and prevents formation of free radicals. Intravenous adenosine has been proven beneficial in AMISTAD,[4] (and AMISTAD II) trials. In AMISTAD trial, effect of adenosine v/s placebo, when given in addition to thrombolytic therapy, was assessed. Cardiac SPECT scan was used to quantify the size of infract. 236 patients were included in study and were randomly assigned to either adenosine infusion at 70mcg/kg/min, given via peripheral venous access for three hours or placebo. Relative reduction in infarct size with adenosine was 33% (*p*=0.03) in all patients, with most benefit seen in patients with Anterior wall MI having 67% relative reduction (*p*=0.014).

Calcium Channel Blockers: Improve coronary blood flow via endothelium dependent and independent mechanisms including vasodilatation and reducing myocardial demand of oxygen via negative chronotropic and negative ionotropic effects. Verapamil, Diltiazem and Nicardipine have been studied in this aspect.

In a recent meta-analysis comparing 7 drug classes for the treatment of no reflow, intracoronary verapamil was the 2nd most efficacious agent after anisodamine in improving TIMI flow grade, according to SUCRA analysis.[5]

Previous Meta analyses have also supported role of verapamil and diltiazem or verapamil alone for the treatment of no reflow.[6]

Nitroprusside: is a direct nitric oxide donor and acts by activating guanyl cyclase. It causes potent vasodilatation, decreases arteriolar resistance, inhibits platelet aggregation and inflammation, thus improves coronary flow.

In a study comparing nitroprusside to nicorandil for the treatment of no re flow in treatment of acute myocardial infarction, nitroprusside significantly improved coronary blood flow in terms of improved TIMI frame counts.[7] Rezkalla, S.H *et al*. also advocated the use of nitroprusside and adenosine in preference to other drugs, for the treatment of no-reflow.[8]

Other Agents

Epinephrine: In the recent COAR trial, intracoronary epinephrine showed to have more efficacy and comparable safety when compared to adenosine for treating no reflow.[9]

Glycoprotein IIb/IIIa Inhibitors: In patients undergoing primary PCI, abciximab treated group showed significant reduction in no reflow phenomenon when compared to those treated with adenosine or normal saline (7%, 13% and 17% respectively). Also, there was decrease in LV remodeling at 6 months in abciximab treated group.[10]

Nitroglycerine: can be beneficial when no reflow occurs due to spasm of epicardial artery.

Aspiration thrombectomy: In the TAPAS trial and its follow-up, thrombus aspiration in addition to conventional primary PCI v/s primary PCI alone, improved myocardial reperfusion, and reduced cardiac event rate at 1 year (3.6% v/s 6.7%).[11] Hassan *et al*. concluded that in presence of high-grade thrombus, thrombus aspiration can help preventing no- reflow.[12]

LIMITATIONS OF STUDY

A case series/RCT to determine refractory no-reflow in cardiac catheterization should be carried out to define the role of intra coronary verapamil.

CONCLUSION

No reflow occurs frequently in primary PCI for ST-elevation MI. Prevention and treatment is important to achieve full benefit of reperfusion. No-reflow causes larger infarct and increased cardiac death at 1 year, as described above. Prevention of no-reflow can be done by shorter door to balloon time, and shorter balloon inflations. Treatment with boluses of intracoronary adenosine and nitroprusside in boluses of 100 microgram is useful and for refractory no-reflow, intracoronary verapamil and epinephrine in boluses of 100 microgram are beneficial. These drugs can be delivered via guiding catheter or via a micro catheter or distal balloon inflated at lesion. Mechanical aspiration of thrombus should be done in cases of heavy thrombus burden. Epicardial artery spasm responds to intracoronary nitroglycerine. Thus, identifying the cause of no-reflow and treating it accordingly will enhance coronary perfusion and improved outcomes. Future directions include use of IVUS and OCT to confirm a specific cause and improve outcomes.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

SSK: Manuscript writing, concept and editing

SN: Study design, concept and critical review

AAC: Intellectual contribution, concept and final approval

AF: Idea, concept, proof reading

HMS: Review of article, formatting and critical review

WA: Proof reading, Intellectual contribution, final approval

MI: Analysis, interpretation and proof reading

BS: Data management, data collection & manuscript writing

AZ: Drafting the manuscript, proof reading and critical

AY: Review of article, formatting and critical review

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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