Clinical research

Non-pharmaco, non-invasive management of coronary no-reflow phenomenon

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Abstract

Introduction: No-reflow is an infrequent but dreaded complication of percutaneous coronary intervention (PCI), where the culprit is obstruction of the downstream microvascular bed. The aim of this study was to evaluate the efficacy and safety of forceful injection of blood (autologous blood transfusion – ABT) in reversing no-reflow during PCI because data regarding its effectiveness is not available.
Material and methods: 100–120 ml of blood was withdrawn through guiding catheter over 3 to 5 min using a 10 ml syringe and re-infused by forceful injection over 3 min through it, and its efficacy was assessed at 10 min using TIMI flow grade and quantitative corrected TIMI frame count.
Results: In total 93 patients received ABT following no-reflow. Their clinical presentation was ST-elevation myocardial infarction (STEMI) (n = 61; 65.6%), non-ST-elevation myocardial infarction (NSTEMI) (n = 23; 24.7%), and unstable angina (n = 9; 9.6%). It was observed among patients undergoing primary PCI (n = 18; 19.3%), pharmaco-invasive PCI (n = 27; 29%), rescue PCI (n = 11; 11.8%), and PCI for cardiogenic shock (n = 5; 5.3%). A mean volume of 108 ±4 ml blood was transfused. Commonest culprit vessel was left anterior descending artery (n = 51; 54.8%) followed by right coronary (n = 29; 31.2%), left circumflex (n = 19; 10.8%), and saphenous vein grafts (n = 3; 3.2%). Following ABT, TIMI 3 flow was successfully restored in 77 (82.7%) patients. TIMI flow grade improved from 1.02 to 2.52 and cTIMI frame count decreased from 60.6 ±12 to 16.1 ±6 (p < 0.001). ABT was well tolerated except transient hypotension (n = 17; 18.3%). Overall mortality was reported in 10 (10.7%) patients at 1 year.
Conclusions: In this largest and only study to date, ABT is a safe and highly effective approach to reverse no-reflow by raising driving pressure across the capillary bed.

Key words: percutaneous coronary intervention, acute coronary syndromes, TIMI frame count, TIMI flow, autologous blood transfusion, no-reflow.

Introduction

Restoration of patency of the culprit artery (infarct related artery) and re-flow of blood in the vessel occluded by thrombus by either pharmacological means using thrombolytics or mechanical means using percutaneous coronary intervention (PCI) is the gold standard of treatment in acute coronary syndrome [1, 2]. Primary PCI successfully restores TIMI 3

flow (thrombolysis in myocardial infarction) in over 90% of patients. However, it restores only epicardial patency because there are small subsets of patients in whom myocardial reperfusion remains impaired despite successful restoration of patency of infarct-related artery (IRA). This is defined as no-reflow phenomenon (also known as slow flow, slow re-flow, low flow), which is largely attributed to severe microvascular obstruction (MVO) of the downstream bed [3]. Its incidence is 7% among patients undergoing rotablation, 12% with primary angioplasty, and as high as 42% for intervention of degenerative graft vessel [4]. Downstream embolisation of thrombi and plaque components during PCI mainly contribute to MVO. However, certain physical factors like spasm, edge dissection, or thrombus need to be excluded before labelling no-reflow phenomenon. It negatively affects the remodelling of infracted myocardium and may lead to hypotension, various tachy-brady arrhythmias, heart failure, and death [5–8]. Reduction of thrombus burden and its downstream migration either by mechanical means like thrombosuction or pharmacological interventions using GP IIb/IIIa antagonists, adenosine (both intracoronary and intravenous), nicorandil (intravenous and intracoronary), verapamil (intracoronary), and nitroprusside have been shown to have variable success [3]. Pharmacological agents have been shown to reduce infarct size principally through coronary vasodilatation and its anti-inflammatory effects by reducing platelet activation, calcium overload, anti-oxidant action, and neutrophil inhibition [9]. Mechanical obstruction from emboli originating from upstream lesions during PCI may produce antegrade resistance to arteriolar flow, which may lead to no-reflow. Forceful injection of blood through a guide catheter helps to reverse the downward spiral of no-reflow by raising the driving pressure across the capillary bed [10].

The goal of this study was to evaluate the efficacy and safety of forceful injection of blood (autologous blood transfusion – ABT) in reversing no-reflow during PCI, because data regarding its effectiveness is not available. Primary endpoints regarding its efficacy were improvement in TIMI flow grade (achievement of TIMI 3 flow) and corrected TIMI frame count (cTFC). Safety endpoints were the absence of periprocedural complications (dissection, hypotension, air embolism) and cardiovascular endpoints (composite of stroke, acute coronary syndrome, and cardiac death) and major adverse cardio cerebrovascular events (MACCE; composite of cardiovascular (CV) events and all deaths) [11].

Material and methods

Study design and participants

This was a prospective, observational study conducted among patients who developed no-reflow following PCI for various indications between May 2017 to December 2018 at LPS Institute of Cardiology, GSVM Medical College, Kanpur, UP, India. The indication for intervention was acute coronary syndrome which included (a) ST segment elevation myocardial infarction (STEMI) incorporating primary, pharmaco-invasive, cardiogenic shock, and rescue PCI; (b) non-ST segment elevation myocardial infarction (NSTEMI); and (c) unstable angina (UA). Baseline demographics of patients, which included clinical (age, sex, clinical presentation and indication for intervention) and angiographic features and procedural data, were recorded. Lesions were classified as type A, B1/B2, or C as per American Heart Association/American College of Cardiology (AHA/ACC) criteria [12]. The presence of collaterals (either ipsilateral or contralateral) to the infarct-related artery was graded using Rentrop grading on basal angiograms [13].

All procedures were performed after obtaining written, informed consent from all patients, and the study protocol was approved by the institutional ethical committee (GSVM Medical College EC- 81/March/2017). Major exclusion criteria for PCI were intolerance to antiplatelet agents (aspirin, clopidogrel, ticagrelor, prasugrel), heparin, expected major surgery within 6 months following PCI, life expectancy < 12 months, and pregnancy.

Procedural details

The procedures were performed through either transfemoral or transradial route following standard techniques using unfractionated heparin on a weight-based regime (70–100 U/kg) as an anticoagulant. Lesion modification was done except in cases of direct stenting where the lesion appeared very soft (thrombus laden) and post dilatation was performed accordingly. In the case of multi-vessel involvement in a patient with acute coronary syndrome (ACS), only the infarct-related artery was intervened during index hospitalisation. All patients were pre-treated with aspirin (325 mg) and P2Y12 inhibitors (ticagrelor, prasugrel, or clopidogrel), and dual antiplatelet (DAPT) agents were continued for at least 12 months followed by aspirin alone indefinitely. The preferred antiplatelet agent was ticagrelor, followed by prasugrel and clopidogrel depending on economy and drug availability. All patients were followed up clinically (history, electrocardiogram, and echocardiogram) at 1 week, 1 month, 6 months, and 12 months, and check angiogram was performed only if symptomatic or when they presented with acute coronary syndrome. Target vessel-related myocardial infarction (MI) was attributed to the target vessel or could not be related to another vessel on the basis of clinical presentation, laboratory data, and electrocardiogram and angiograph-

ic findings [14]. Revascularisation was performed when the diameter of stenosis was ≥ 70% along with subjective evidence of ischaemia.

Assessment of coronary flow in the catheterisation laboratory

All angiograms were reviewed and graded independently by two interventional cardiologists to assess TIMI flow grade in accordance with the TIMI before intervention, at the onset of no-reflow, and at the end of the procedure [15]. Vasospasm, edge dissection, or thrombus were ruled out before labelling as no-reflow phenomena. Angiographic flow was assessed using corrected TIMI frame count method (cTFC) [16]. All cine angiograms were recorded at 30 frames/s with a field size that enabled visualisation of both entry of contrast into the culprit artery and its runoff from a distal landmark. It was analysed by another independent investigator in random order, who was unaware of the sequence of injections. The initial frame used for the TFC was the first frame in which contrast fully enters the artery, whereas last frame was defined as the frame when contrast first entered the branch most distal to the culprit lesion. The number of cine frames between the first and last frames was measured to determine the TFC. Intra-observer variability was assessed with two separate readings, which was ±5 frames. The cTFC was compared before and after autologous blood transfusion.

Protocol of autologous transfusion

In case of coronary no reflow, 100–120 ml of blood was withdrawn from the side port of a small extension tube attached to side arm of a Y-connector using multiple 10 ml syringes over a 3- to 5-minute period with the guidewire kept in situ. All syringes were carefully de-aired and then blood was forcefully injected from the side port of Y-connector over a 3- to 4-minute period using handheld syringes. The force of injection is subjective, but it should be little more forceful than what one uses for routine contrast injection and should be enough to finish infusion of blood over 3–4 min. The amount of blood required to be infused was decided based mainly on the calibre of vessel and site of stent placement. In a medium sized vessel (> 3 mm) with proximal stent, nearly 120 ml of blood was infused while in a medium to smaller size vessel with shorter stent at mid segment of the artery, 80 ml was infused. Electrocardiogram and vitals were closely monitored. In the case of transient hypotension, intravenous fluid was infused. TIMI flow and cTFC were finally re-assessed after 10 min. Procedural success was defined as attainment of TIMI 3 flow. In the case of no response from ABT, standard measures like intracoronary verapamil, sodium nitroprusside, adenosine, and nicorandil were used after 15 min.

Statistical analysis

Statistical analyses were performed using SPSS 19.0 (SPSS Inc., Chicago, IL, USA). Normally distributed data were presented as the mean ± standard deviation (SD). Categorical data were recorded as percentages. Differences in cTFC before and after ABT were analysed using the χ^2 test. A probability level of $p < 0.05$ was considered statistically significant.

Results

Patient and lesion characteristics

During the index period 93 patients experienced no-reflow phenomenon, who were treated using ABT, among 1982 interventions performed. Baseline clinical and angiographic characteristics are shown in Table I. The patient population consisted of 66 (71%) men and 27 (29%) women, with a mean age of 53.4 ±17.9 years. The commonest risk factor was smoking (n = 228; 31.9%) in the form of either cigarette or bidi (n = 29; 31.2%) followed diabetes (n = 24; 25.8%) and hypertension (n = 23; 24.7%). Indications for PCI were STEMI (n = 61; 65.6%), NSTEMI (n = 20; 21.5%), UA (n = 09; 9.6%), and graft vessel (n = 03; 3.2%). The left ventricular ejection fraction was severely impaired in 18 (19.3%) patients, while it was relatively preserved in 55 (59.1%) patients. The culprit vessel was left anterior descending artery in 51 (54.8%) patients, left circumflex artery in 10 (10.8%), right coronary artery in 29 (31.2%), and saphenous vein grafts in 3 (3.2%) patients. All grafts were degenerated (mean vein graft age: 13.3 ±2.1 years). Target lesions were typically high risk (ACC/AHA class B2 or C lesions) in 78 (83.9%) patients and mostly complex, and thrombotic (Table II).

Procedural details

The average delay from the beginning of symptoms to start of intervention was 6.2 ±3.5 h in patients with primary PCI, NSTEMI, and UA and 32.4 ±12.6 h and 24.6 h in patients with rescue and pharmaco-invasive PCI, respectively. Collaterals to the culprit artery were observed in 23 (24.7%) patients, who were labelled as grade 3 in 10 (10%), grade 2 in 11 (12%), and grade 1 in 2 (2.7%) patients. Thrombus aspiration was performed using a Thrombuster II (Kaneka Medical; Japan) aspiration catheter in 10 (20.4%) patients who had acute total occlusion. Partial restoration of flow (TIMI 1/TIMI 2) was observed in all 38 patients who had total occlusion at baseline (Figure 1). All lesions

Table I. Baseline, clinical, and angiographic characteristics of patients (n = 93)

Characteristics	*N* (%)
Age [years]	53.4 ±17.9
Male	66 (71)
Female	27 (29)
CAD risk factors:	
Hypertension	23 (24.7)
Diabetes mellitus	24 (25.8)
Smokers (cigarette/bidi/smokeless tobacco)	29 (31.2)
Family history of CAD	4 (4.3)
Dyslipidaemia	20 (21.5)
Clinical presentation:	
STEMI:	61 (65.6)
Primary	27 (29)
Pharmaco-invasive	18 (19.3)
Cardiogenic shock	5 (5.3)
Rescue PTCA	11 (11.8)
NSTEMI	20 (21.5)
UA	9 (9.6)
Graft Vessel PCI	3 (3.2)
LVEF:	
> 45%	55 (59.1)
35–45%	20 (21.5)
< 35%	18 (19.3)
Medications:	
Aspirin	90 (96.8)
Clopidogrel	54 (58.1)
Prasugrel	24 (25.8)
Ticagrelor	15 (16.1)
Statin	90 (96.8)
β-blocker	67 (72)
ACEI/ARB	74 (79.6)
Ivabradine	6 (6.4)
Aldosterone antagonist	22 (33.7)
Angiographic severity of CAD (Target vessel location):	
SVD	49 (52.7)
DVD	23 (24.7)
TVD	21 (22.5)
Culprit lesion location:	
LAD	51 (54.8)
RCA	29 (31.2)
LCx	10 (10.8)
SVG	3 (3.2)

Data presented as mean ± standard deviation or number (percentage). CAD – coronary artery disease, DM – diabetes mellitus, PCI – percutaneous coronary intervention, STEMI – ST-segment elevation myocardial infarction, NSTEMI – non-ST segment elevation myocardial infarction, UA – unstable angina, LVEF – left ventricular ejection fraction, ACEI – angiotensin-converting enzyme inhibitor, ARB – angiotensin-receptor blocker, SVD – single-vessel disease, DVD – double-vessel disease, TVD – triple-vessel disease, LAD – left anterior descending coronary artery, LCx – left circumflex coronary artery, RCA – right coronary artery, SVG – saphenous vein grafts.

Table II. Procedural characteristics and outcome of patients (n = 93)

Variables	Values, *n* (%)
AHA/ACC lesion class:	
A	2 (2.1)
B1	13 (13.9)
B2	68 (73.1)
C	10 (10.8)
Lesion characteristics:	
Ulcerated	13 (13.9)
Thrombus	68 (73.1)
Acute total occlusion	38 (40.8)
Dissection	5 (5.3)
Collaterals present (grade 1–3)	23 (24.7)
Size of vessels [mm]:	
2.25–2.5	21 (22.5)
2.5–3	30 (32.3)
3–3.5	33 (35.4)
3.5–4 mm	9 (9.8)
TIMI flow pre procedure:	
Grade 0	39 (41.9)
Grade 1	25 (26.8)
Grade 2	17 (18.4)
Grade 3	12 (12.9)
Median length of stent per patient [mm]	36 ±12
Procedural details:	
Lesion modification:	
Direct stenting	10 (10.8)
Thrombosuction	19 (20.4)
Predilatation (semi/noncompliant balloon)	83 (89.2)
GP IIb/IIIa antagonist	21 (22.5)
Post-dilation	80 (86)
Amount of blood used for autologous transfusion [ml]	98 (80–130)
Transient hypotension	17 (18.3)
Dissection, air embolism	0 (0)
CV end points:	11 (11.8)
Cardiac death	9 (9.7)
ACS	2 (2.1)
Stroke	0 (0)
MACCE	12 (12.9)
TLR	2 (2.1)
Stent thrombosis	4 (4.2)
Corrected TIMI frame count (Pre ABT)	53.6
Corrected TIMI frame count (Post ABT)	16.9
TIMI flow post procedure:	
Grade 0	0 (0)
Grade 1	3 (3.2)
Grade 2	13 (14)
Grade 3	77 (82.8)

CV end points – cardiovascular end points, MACCE – major acute cardio cerebrovascular events – composite of CV events and all deaths, TLR – target lesion revascularisation.

were predilated except in 10 patients (10.7%) who had a discrete ulcerated lesion where direct stenting was performed (Table II). GP IIb/IIIa antagonist (Tirofiban) was used after balloon dilatation in 10 (10.8%) patients, while 14 (12.5%) patients received it after stent deployment following onset of no-reflow. No-reflow occurred initially after stent deployment in 66 patients, and post-stenting balloon dilatation in 37 patients, of whom 56 (60.2%) had TIMI 1 flow while 37 (39.8%) patients had TIMI 2 flow (Figure 1).

A mean dosage of 96 ml of blood was forcefully injected (median: 112 ml, range: 80–130 ml). TIMI flow grade and cTFC after no-reflow and following ABT is shown in Figures 2 and 3. A significant improvement in TIMI flow grade was observed after ABT ($p < 0.01$). TIMI flow grade improved from 1.02 to 2.52 after ABT with successful restoration of TIMI 3 flow in 77 (82.8%) patients while TIMI 2 flow was restored in 16 (17.8%) patients. Therefore, the overall success rate of ABT was 86%. No-reflow was successfully reversed in all 3 (100%) patients with vein graft, and 74 of 90 patients (82.2%) among native vessel intervention. Patients with the lowest TIMI flow grade after PTCA showed the most extensive improvement of coronary flow (Figure 1). Similarly, TIMI frame count decreased from 62 ±12 at the time of no-reflow to 18 ±6 after ABT ($p < 0.001$), with an improvement of 44 ±7. In native vessels it decreased from 60 ±10 to 17 ±5 following ABT ($p < 0.001$), while in venous bypass grafts the TIMI frame count decreased from 64 ±16 to 22 ±8 after ABT ($p < 0.01$). A typical no-reflow situation of totally occluded RCA in a patient presenting with acute IWMI and its successful reversal with ABT is shown in Figure 4.

In-hospital and follow-up outcome

In three patients with no-reflow, two patients had partial restoration of flow (TIMI 2) following intracoronary administration of sodium nitroprusside. They were discharged after 10.2 ±2.2 days. The remaining patient with no-reflow was later mechanically ventilated because of progressive heart failure, and he later succumbed on the fifth day. However, no re-infarct or stent thrombosis were reported during index hospitalisation. On follow-up, CV events were reported in 11 (11.8%) patients, which was primarily driven by cardiac death ($n = 9$; 9.7%). Overall death was 9.7%, while death among patients who had presented with cardiogenic shock was 20% ($n = 1$). Two patients presented with STEMI as a result of late stent thrombosis, who underwent successful revascularisation. Malignant arrhythmia ($n = 4$; 44%) and progressive pump dysfunction ($n = 5$; 56%) were reasons for all cardiac death. MACCE was reported among 12 (12.9%) patients

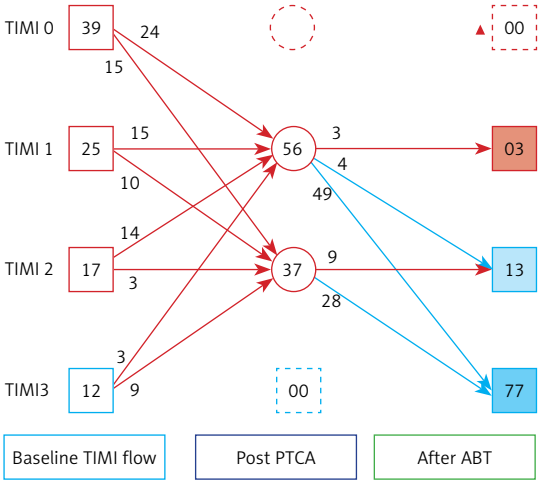

Figure 1. Changes of TIMI flow grading at baseline, after deployment of stent (all patients had TIMI flow grade < 3), and following ABT, which led to its improvement to either TIMI 2 or TIMI 3 flow grade

Discussion

The present study, the first of its kind to date, demonstrated the safety and efficacy of forceful injection of blood through a guiding catheter (au-

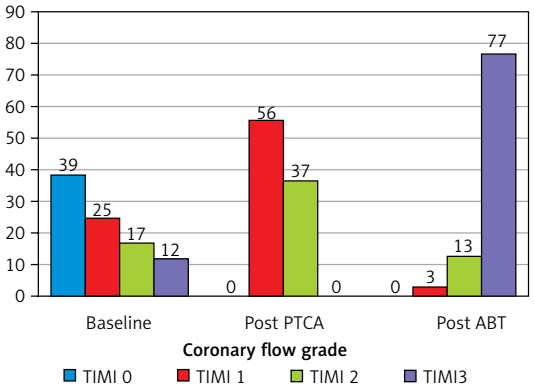

Figure 2. Changes of TIMI flow grading at baseline, after deployment of stent and after ABT. There was significant improvement in TIMI flow following ABT ($p < 0.001$) because TIMI flow was impaired in all patients prior to treatment

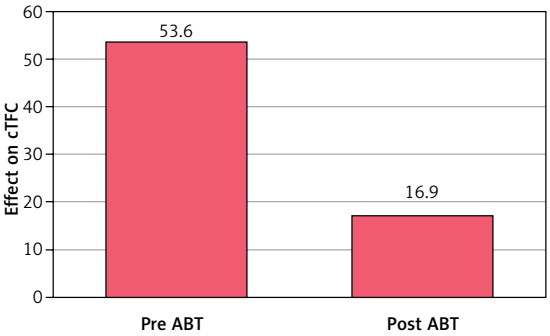

Figure 3. cTFC at the time of no-reflow and after ABT showing significant reduction in TIMI frame count ($p < 0.001$)

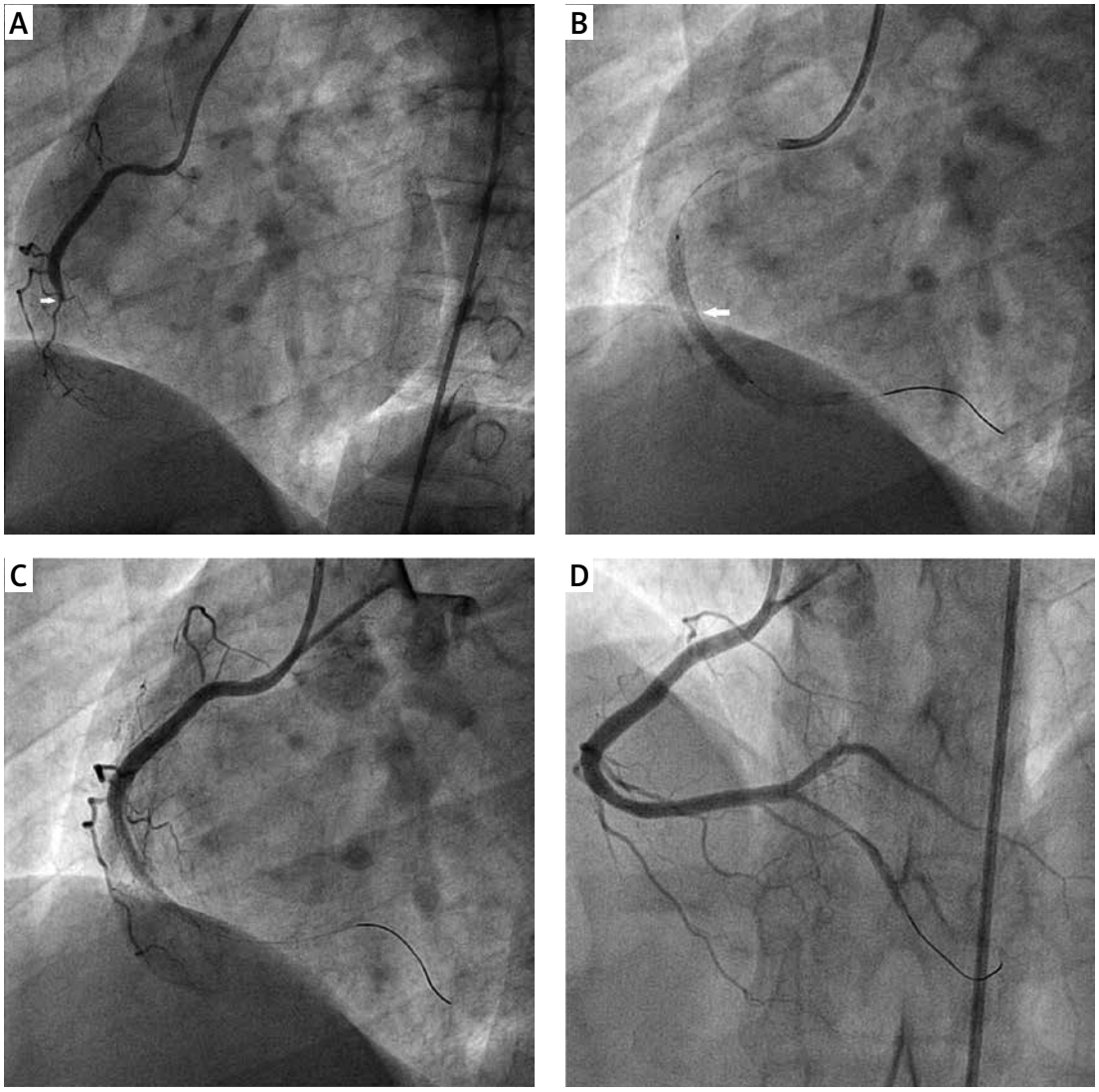

Figure 4. Left anterior oblique view showing totally occluded mid right coronary artery (**A**), it was stented with 3.5 × 28 mm Xience Prime (Abott Vascular; USA) after deploying at 13 atm pressure (**B**), no reflow of RCA following stent deployment (**C**), TIMI 3 flow of RCA after forceful injection of blood (**D**)

tologous blood transfusion) for reversal of no-reflow during PCI for acute myocardial infarction. This adjunctive measure was quite safe and effective at addressing the no-reflow (overall success rate – 82.8%), and it did not require any pharmacological intervention, thereby negating any untoward side effects, and it was a readily available option. It works not only for native vessels but also for venous grafts. There are several mechanisms of phenomenon of no-reflow, and therefore there are multiple preventive and therapeutic strategies, both pharmacological as well as mechanical, but guidelines are still lacking. This lessens the advantages of open artery and also increases the risk of future cardiovascular events, and it has been associated with worse clinical outcomes. Microvascular obstruction (size ≥ 200 µm) is the culprit and may result from clogging by atherosclerotic debris because of hardware manipulation. Underlying microvascular dysfunction, thrombus burden, and retrograde perfusion by collaterals, diabetes, and dyslipidaemia are among the exacerbating factors.

In our study, the success rate of ABT (82.8%) was comparable to other pharmacological measures like intracoronary administration of the combination of adenosine and nitroprusside, adenosine alone, calcium channel blockers (nicardipine, diltiazem, verapamil), vasodilators (nicorandil, sodium nitroprusside), and epinephrine, the success rate of which varies from 65% to 95% [17]. The various side effects with these agents are atrio-ventricular block, ST elevation or ST depression, need of temporary pacing wire, or atropine occurring in various proportions.

Adenosine, a purine nucleoside, although effective for no-reflow, has very rapid clearance because it has a half-life of 6 s and therefore may require multiple administration, which is time

consuming and costly. Also, it causes bronchospasm, chest pain, hypotension, and transient atrioventricular block [18, 19]. ABT, in contrast to adenosine, is a one-time affair and is not associated with these side effects.

Nicorandil has the dual property of nitrate donor and ATP-sensitive potassium channel-opener, which acts on the micro-resistance vessel causing vasodilatation. It is helpful in combating no-reflow but has no action on aorto-coronary vein grafts, which might be a disadvantage, while our study has shown the effectiveness of ABT in this substrate of patients, as well [20–22].

Similarly, calcium channel blockers (nicardipine, diltiazem, verapamil) are also effective, but a major concern is the various degree of atrio ventricular block and hypotension. In this regard, ABT is superior and safer because no rhythm disturbance was noted [23–25].

Overall mortality over 12-month follow-up was concordant with Werner *et al.* [23], who reported it to be around 10%. Our finding was also similar to results among patients who had presented with cardiogenic shock.

In our study, ABT was quite safe, although transient hypotension was reported in 18%, which was reversible. The possible reason for its beneficial effect is increased driving pressure across the capillary bed, which helps clear the microvascular bed of debris, thus restoring the flow. As the density of erythrocytes and neutrophils decreases across the capillary bed, reactive oxygen species-mediated endothelial damage, inflammation, and interstitial oedema does not happen, which helps to achieve TIMI 3 flow. As the spiral of multiple factors culminate into the final phenomena of no-reflow, its treatment is multiple. As the clogging of microvascular bed is quickly cleared, the chain reaction of inflammatory cascade turning into endothelial injury and intramural haemorrhage does not occur. Or study has a complex substrate of patients, although graft vessel intervention was less, but even in this small group it was 100% successful. Therefore, we speculate that it may show its benefit in a larger cohort, as well. In our study, 22.5% of patients received GP IIb/IIIa antagonists, and they benefitted from this therapy.

Although this was a prospective study of consecutive patients in whom no-reflow was observed, this was a nonrandomised study (lack of control group), had small number of patients, was observed in background of acute myocardial infarction only, and had no long-term follow-up. Moreover, acute gain in TIMI flow following forceful injection of blood confirmed its efficacy. However, one might opine about spontaneous resolution of no-reflow after prolonged observation over an extended period of time, but considering the background of AMI where the earliest attainment of TIMI 3 flow is the gold standard, it was not considered. Because this is the first study to be reported, it warrants further evaluation in larger randomised controlled trials.

In conclusion, the phenomenon of no-reflow is not uncommon, especially in the setting of primary percutaneous coronary intervention or intervention of bypass graft. Our study, the first ever to be reported, demonstrated the efficacy and safety of forceful injection of blood in reversing no-reflow. This modality will be newer therapeutic option in the armamentarium for the treatment of no-reflow in the catheterisation laboratory.

Conflict of interest

The authors declare no conflict of interest.

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