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Effect of Intravenous Abciximab on Coronary Flow Improvement After Re-vascularization in Primary Coronary Intervention and Short Term Impact

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ABSTRACT

Introduction: Of recognized fact the importance of early diagnosis and early management of ST-elevation myocardial infarction, to regain a normal or at least adequate coronary flow in the Primary Percutaneous Intervention. Slow or no-reflow is suboptimal myocardial reperfusion, without angiographic evidence of mechanical obstruction. Adenosine, Verapamil and saline flush are manoeuvres proved useful. The resolution of ST-segment is associated with successful revascularization and regarded as a predictor for future events. Glycoprotein IIB/IIIA inhibitors are a group of anti-platelets widely used in acute coronary syndrome. **Aim:** The aim of the study was to investigate that: uses of intra venous Abciximab, does not improve coronary flow in patients with MI that develop sub optimal flow after primary PCI within 30 minutes, but the improvement need 12 to 24 hour as founded in other studies, and its beneficial effect is related to early improvement in LV function and decrease of re-infarction and re-hospitalization. **Method:** Prospective, case-control study, enrolled fifty patients randomly assigned into two matching groups, first group (25 patients) received an intravenous Abciximab while the second group (25 patients) received intracoronary saline flush. Repeated angiography after 30 minutes, for immediate resultant flow assessment, Electrocardiographic changes resolution, bleeding and death. After a 30 days, a clinical assessment for primary outcome including, death, recurrent Myocardial infarction and Heart failure While the Secondary outcome including stent thrombosis, target vessel revascularization in addition to the primary outcome. **Result:** There was no significant difference in the flow Improvement and ECG resolution between both groups. These findings not affected by the door to balloon time. However, patients with flow improvement had a significant resolution in their ECG. Bleeding propensity and mortality were not significantly affected. Literatures proved the benefit of Abciximab in acute coronary syndrome. **Conclusion**: Both intravenous Abciximab and intracoronary saline flush had comparable effect on coronary flow improvement post primary percutaneous intervention, with minimal variation in the bleeding and in-hospital mortality.

Keywords: intravenous Abciximab, slow flow, primary coronary intervention.

1. INTRODUCTION

Although coronary revascularization is the main target in myocardial infarction (MI) management, however, it is not always achieved. When available, percutaneous coronary intervention (PCI) that uses balloon angioplasty, with or without stenting, is the standard treatment for ST-segment elevation myocardial infarction (STEMI) (1). However, several patients do not get benefit appropriately from Expedite revascularization for total occlusion, as they don't show resolution of the signs of ischemia like electrocardiographic (ECG) changes and flow abnormality (2). These patients also exhibit an angiographic phenomenon evidenced with slow-flow in the affected vessel (Thrombolysis in Myocardial Infarction (TIMI) flow less than 3) and lack contrast uptake i.e., "blush" by the subtended myocardium, resulting in a potential dissociation between coronary revascularization (which was relieved) and myocardial perfusion in STEMI (3).

Mechanism and Pathogenesis of No-Reflow

This special phenomenon is still not fully understood. However, several theories were generated to explain it. Originally, it was believed that prolonged ischemia with extensive myocardial damage results in microvascular (capillary bed) distraction, causing incomplete reperfusion. Recently, other factors were believed to play a role in these phenomena of no-reflow, specif-

ically distal embolization of the plaque/thrombus after balloon inflation. This theory was helped by the observation that patients with no-reflow were significantly had a greater quantity of embolic material (platelet–fibrin complexes, macrophages, and cholesterol crystals) trapped in the distal protection device if they compared to patients with normal reflow (4). Other factors play a role partially; in the pathogenesis of no-reflow involve platelet/endothelial activation with systemic inflammatory response, microvascular vasoconstriction and myocardial edema, calcium overload, and oxygen-derived free radicals. Systemic potentiating of inflammatory cells might enhance no-reflow, as seen by the observation of raised serum levels of C-reactive protein (CRP) which was associated with impaired coronary microvascular response to endothelium-dependent and independent vasodilator stimuli (5-6) and also with enhanced trans-cardiac Neutrophil activation (7). Platelets might be involved in no-reflow by several mechanisms, like microvascular obstruction by platelet aggregates and release of platelet-derived vasoactive with chemotactic mediators (8).

So no-reflow can be divided to four main pathogenic subsets:

- Distal athero-thrombotic embolization.
- Ischemia-related injury.
- Reperfusion-related injury.
- The susceptibility of coronary microcirculation to injury (9).

Although the exact mechanism of no-reflow stays unknown, it is most likely complex and multi-factorial. According to the previously mentioned theories, multiple possible predictors of no-reflow have been investigated. Age, smoking, previous myocardial damage, time-to-treatment interval, serum creatinine, left ventricular ejection fraction (LVEF), preinfarction Killip class, CRP, baseline TIMI flow grade, B-type natriuretic peptide (BNP), and initial perfusion defect all can predict the development of no-reflow (10-11). Because of the suggested role of platelets in induction and continuation of no-reflow, mediators that affect platelet activation, such as Thromboxane A2 (TXA2), might have a role in no-reflow. TXA2 is an important mediator of platelet activation and aggregation and considered an important mediator of platelet-induced coronary arterial constriction (12).

Impact and Prognosis of No-Reflow

The development of the no-reflow phenomenon is a poor prognostic sign. It is associated with a significant reduction of the myocardial salvage with primary PCI among patients with STEMI. As reduced myocardial salvage results in more myocardial necrosis, no-reflow effects left ventricular function and increases mortality, this was evident at six months (13). One-year mortality was 16.7 % in patients with no-reflow versus 5.5 % in patients who had normal flow. Six months follow-up angiography for patients with no-reflow cleared that only 20% continued to have slow TIMI flow, with normalization of TIMI flow in 80 % of patients. Patients with no-reflow after primary PCI who regain normal blood flow in the six-month angiography had a significantly better LV function than those with suboptimal blood flow persisted six months after primary PCI. Long-term prognostic data have been published (14) and confirmed the persistent poor prognostic effect of no-reflow causing an increase in five-year mortality from 9.5% to 18.2 % (15).

Glycoprotein IIb/IIIa inhibitors

There is strong randomized trial data about clinical outcomes of IIb/IIIa inhibitors use in the setting of ST-elevation MI (16) were its use in this setting is a Class IIa indication in the 2017 PCI guidelines (17). Possibly one mechanism of benefit is a reduction in the no-reflow when patients treated with IIb/IIIa inhibitors. According to 2017 ESC guidelines pre-hospital routine use of glycoprotein (GP) IIb/IIIa inhibitors before primary PCI has no benefit and increases bleeding risk if compared with use in the catheterization laboratory (18).

2. AIM

The aim of this study was to investigate that: uses of intra venous Abciximab, does not improve coronary flow, in patients with MI that develop sub optimal flow after primary PCI within 30 minutes, but the improvement need 12 to 24 hour as founded in other studies, and its beneficial effect is related to early improvement in LV function and decrease of re-infarction and re-hospitalization.

3. PATIENTS AND METHODS

During the period from December 2018 to October 2019, total 411 patients presented with acute MI and underwent primary PCI, 70 of them (17%) developed slowly or no flow after stenting. Twenty patients were excluded by the exclusion criteria. The remaining 50 patient enrolled in the study and were randomized into two groups, the first group (25 patients) who received Abciximab intracoronary in a dose of 0.25 mg/kg bolus, then 0.123mg/kg over 12 hours, while the second group (25 patients) received intra coronary saline flush. Patients were reassessed after 30 minutes on the table with angiography to detect the response. Early ECG ST Resolution is defined as a reduction more than 50% in the ST–segment magnitude from the baseline after 60 minutes from intervention, while delay after this time considered late. All patients have preloaded with aspirin 300 mg and clopidogrel 600 mg and 5000 unit intravenous heparin before referral and unfractionated heparin during procedure. Patients who had a history of coronary artery bypass grafting, or had a history of fibrinolysis therapy or those needed thrombus aspirations during the procedure, were excluded. The study design, sampling and follow up were described in the included flow diagram.

Statistical analysis

SPSS® Software (version 23.0 for Linux®) was used to perform statistical analysis of the study data. Qualitative data are presented as numbers and percentages, while continuous numerical data are presented as mean ± standard deviation. A comparison of study groups was

carried out using the chi-square test for categorical data and using Student's t-test for continuous data. P-value of < 0.05 was considered statistically significant.

4. RESULTS

Age of population studied ranged from 38 years to80 years, with a mean of 57.5 and58.5 years for Saline flush group and Abciximab group respectively. The age in addition to other demographic characterization showed in Table (1).

Characteristics		Saline flush group	Abciximab group	P value
Mean Age (yrs.) +/- SD		58.1 +/-10.3	57+/- 9.5	0.681
Male Sex		15	16	0.82
History of diabetes no.(%)		10 (40)	13 (52)	0.395
History of hypertension no.(%)		16 (64)	13(52)	0.390
Smoking no.(%)		10(40)	11(44)	0.77
No. of diseased vessels no.(%)	1	14(56)	15(60)	0.68
	2	7(28)	8(32)	
	3	4(16)	2(8)	
Site of infarction	Anterior no.(%)	13(52)	15(60)	0.56
	Non anterior no.(%)	12(48)	10(40)	

Table 1. Demographic characterizationof the studied sample

No statistically significant difference was found between saline flush group and Abciximab group regarding sex, history of diabetes, hypertension, smoking, number of diseased vessels, and anterior infarction compared to non-anterior. Significant if P-value <0.05, regarding the anatomy of related coronary arteries that involved in the myocardial infarction detected during angiography, there was no significant difference between both groups, figure (1).

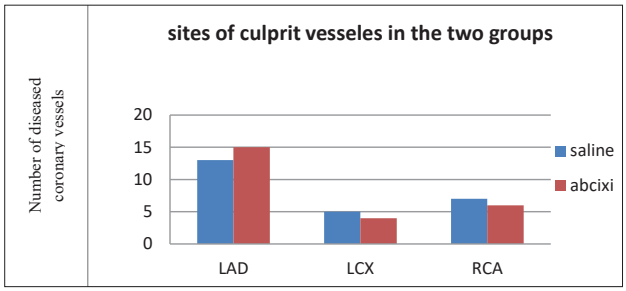

Figure 1. Culprit vessels distribution compared in both groups, no significant anatomical difference P-value=0.84

The patients in the two groups underwent their primary PCI procedures in the recommended pain to balloon time as in Figure 2.

After primary PCI, the resultant improvement in the coronary flow was compared between the two study groups. 40% of saline group had improvement, while 44%in the Abciximab group. There was no statistically significant difference between two groups, p value=0.77 (Figure 3).

The in hospital complications including bleeding, death , re-infarction or rehospitalization were comparable in both groups, although rehospitalization was more in saline group, however it didn't reach level of significance (Figure 4).

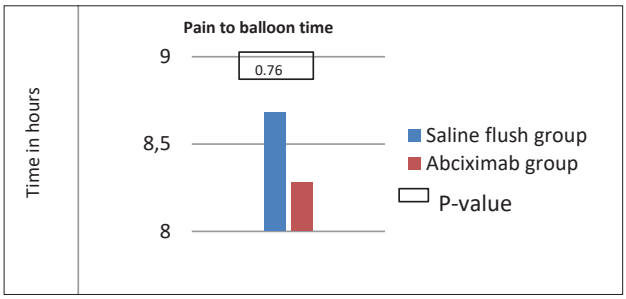

Figure 2. Ccomparison of Pain-to-Balloon time using Student's test had shown non-significant difference between saline group (M=8.7 hours, SD=3.0) and Abciximab Group (M=8.3 hours, SD=2.9); t (48) = 0.525, P-value = 0.76.

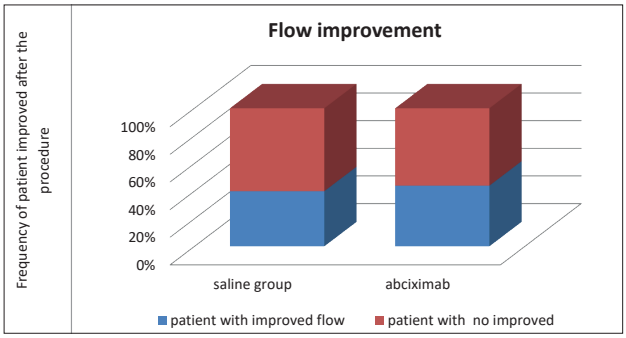

Figure 3. Comparing the frequency percentage for the cases with flow improvement in the two groups. No significant difference detected with P-value 0.77

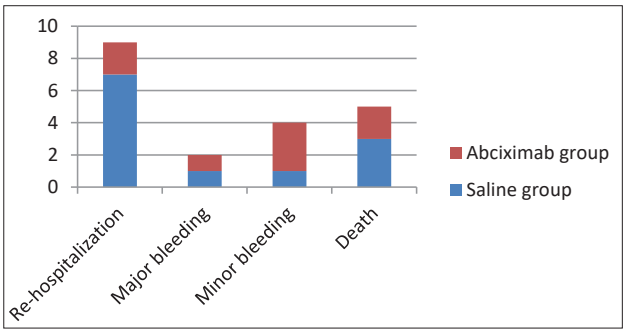

Figure 4. Clinical assessment comparing the two groups shows rehospitalization were more frequent in saline flush group but still not significant , with p value=0.54

Regarding ECG ST-segment resolution post-PCI, there was no significant difference between both groups for early and late resolution of ST-segment, as detailed in Table (2).

During comparison between ECG ST-segment resolution and flow improvement within the saline flush group. There was a statistically significant relationship between the two variables (Table 3).

Similarly, Comparison between ECG ST-segment resolution and flow improvement within the Abciximab group as showed in Table 4. There was a statistically significant relationship between the two variables, Fisher exact P-value = 0.0051.

ECG ST- resolution	Saline Flush, n=25	Abciximab, n(5)	P-value
Early	9 (47)	10(52)	NS
Late	16(51.6)	15(48.4)	NS

Table 2. Pattern of ECG resolution .No significant differences in early and late ECG ST-resolution in both Saline flush and Abciximab groups

Pattern of flow	Late ECG resolution (%) In Saline Group	Early ECG resolution (%) In Saline Group	Total
Improved	2 (12.5%)	8(88.9%)	10(40%)
not improved	14(87.5)	1(11.1)	15(60%)

Table 3. Relation between ECG resolution and flow improvement after saline infusion with Fisher exact P-value = 0.0003.avery high significant relation

Improved flow	Late ECG In Abciximab Group	Early ECG In Abciximab Group	Total
	3(20%)	8(80%)	11(44%)
No flow improvement	12(80%)	2(20%)	14(56%)

Table 4. High significant relation detected between ECG resolution and flow improvement after Abciximab infusion with Fisher exact P-value = 0.0005.

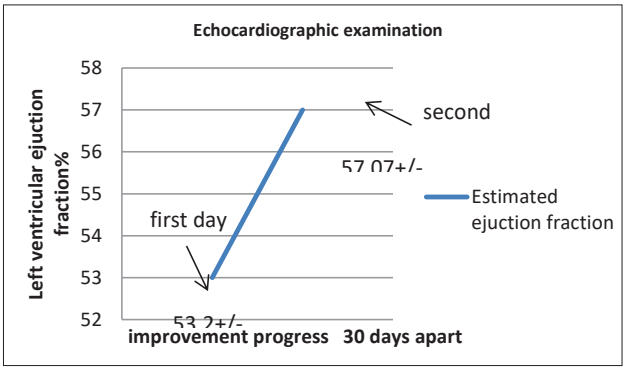

Figure 5. Comparing the Echocardiographic readings for Left ventricular systolic function (mean +/- SD) in the early days of admission with second reading 30 days later in patients had flow improvement.P-value0.002

Patients with improvement in their coronary blood flow after either procedure had a significant improvement in their left ventricular systolic function proved by repeated Echocardiography 30 days later (Figure 5).

5. DISCUSSION

In this study we found that use of Abciximab in patients with suboptimal flow have no significant correlation with flow improvement or early ST resolution, bleeding and early death, on the other hand we found that slow flow was significantly correlated with early and late complication including ST resolution, LV dysfunction and early re-hospitalization that were found in many studies like Poli A et al. that study 114 patients with STEMI that underwent primary PCI and found that TIMI flow associated directly with left ventricular function and inversely with ST segment resolution (19). Kaul U et al. who studied Twenty-one instances of persistent slow flow phenomenon were encountered in 131 consecutive patients subjected to primary PTCA for AMI (16%). It was more common in patients presenting with AMI complicated by Cardiogenic shock (nine of 21, 43%). Of these 21 cases of slow flow, 10 patients were given injection Abciximab during the procedure of primary PTCA as a bail-out measure after encountering the complication of slow flow or no reflow. A pre-discharge coronary angiography was carried out in all patients who survived, in seven of 10 patients in the Abciximab group flow had improved to TIMI-3. In contrast, in the non-Abciximab group TIMI flow improved in only four of 11 patients. Patients with persistent slow flow had significantly higher mortality at the first 30-day follow-up than patients with TIMI-3 flow (33% versus 1.8%, p<0.001) (20). In CADILAC trial which was one of earliest modest size randomized trial that studied Abciximab in primary PCI and PTCA in patients with STEMI compared to placebo found improved early clinical and angiographic outcomes with treatment, they compared early and late results by Abciximab treatment among 2082 patients randomized in an open-label, 2x2 factorial-design trial of primary stenting against angioplasty and Abciximab treatment (n=1052) against no Abciximab treatment (n=1030) concluded that it significantly enhanced 30-day event-free survival (21). Michael Lincoff M.D., et al., for the Evaluation of Platelet IIb/IIIa Inhibition in Stenting Investigators enrolled 2399 patients that randomly assigned to stent implantation and placebo, stent implantation and Abciximab, or balloon angioplasty and Abciximab. The patients followed up to six months concluded significant decrease in re infarction and death at six months in stenting with Abciximab compared to stent and placebo. In European meta-analysis studying Abciximab in primary coronary stenting of ST-elevation myocardial infarction, including The ISAR-2, ADMIRAL, and ACE studies , where the primary endpoint was the composite of death or re-infarction up to 3 years of follow-up. A total of 1101 patients, presenting for primary PCI and stenting of STEMI were randomized to Abciximab (n=550) or placebo (n=55). The primary endpoint of death or re-infarction was significantly reduced from an estimated cumulative hazard rate of 19.0% with placebo to 12.9% with Abciximab [RR (95% IC): 0.633 (0.452; 0.887), P=0.008]. The mortality rate was reduced from an estimated cumulative hazard rate of 14.3% in the placebo arm to 10.9% in the Abciximab arm [0.695 (0.482; 1.003), P=0.052]. Re-infarction was reduced from an estimated cumulative hazard rate of 5.5% with placebo to 2.3% with Abciximab [0.41 (0.203; 0.831), P=0.013]. Major Bleedings were 2.5 and 2% with and without Abciximab, respectively (NS). Still an important limitation to this study is the lack of angiographic assessment of the response of coronary flow to the Abciximab after a 24 hour that was found to be improved by ADMIRAL study were they had significant improvement 24 and sixth months after. INFUS-AMI trial found similar finding making this as solid base for use of Abciximab in primary percutaneous coronary intervention. The use of oral antiplatelet agents has narrowed the indications for Abciximab during PCI for STEMI. The decision to use Abciximab can be guided

in part by the adequacy of availability of aspirin and P2Y12 receptor blockers, which are inhibitors of different pathways for platelet activation. Using GP IIb/IIIa inhibitors as saving therapy in case of angiographic evidence of a large thrombus, slow- or no-reflow, and other thrombotic complications is reasonable (class IIa). Overall, there is no evidence to recommend the routine use of GP IIb/IIIa inhibitors for primary PCI.

Study Limitations: Lacking of control angiography after reasonable time, Small number of patients included in this study may explain other finding detected by other studies.

6. CONCLUSION

In this study we've concluded that: uses of intra venous Abciximab, does not improve coronary flow, in patients with MI that develop sub optimal flow after primary PCI within 30 minutes, but the improvement need 12 to 24 hour as founded in other studies, and its beneficial effect is related to early improvement in LV function and decrease of re-infarction and re-hospitalization.

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