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Thrombus Aspiration Plus Intracoronary Abciximab vs Intracoronary Abciximab Alone in Patients with STEMI Undergoing Primary PCI

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Authors' contributions

This work was carried out in collaboration among all authors. Author PKA designed the study, author KT performed the statistical analysis, author PR wrote the protocol and wrote the first draft of the manuscript. Authors SS and PKA managed the analyses of the study. Authors GR and RBV managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Thrombus embolization during the Percutaneous Coronary Intervention (PCI) in ST-segment elevation myocardial infarction (STEMI) is common and results in suboptimal myocardial perfusion and increased infarct size. Two strategies proposed to reduce distal embolization and improve outcomes after primary PCI is bolus intracoronary Abciximab and manual aspiration thrombectomy. There are several factors which influence the decision of primary PCI in a patient with AMI in developing countries. Cost of therapy and affordability is probably the most important factor. The additional cost for thrombus aspiration needs to be considered against the additional advantages in terms of better clinical outcome.

Objectives: To compare the use of a combination of intracoronary Abciximab with manual thrombus aspiration to intracoronary Abciximab alone, in patients with STEMI undergoing primary PCI.

Patients and Methods: This is a prospective observational study of patients with STEMI who underwent primary PCI between June 2018 to May 2019. A pre-approved study protocol was

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designed to determine the eligibility of STEMI patients to be included in the study. Patients with The patients have analysed in two groups: 84 patients received a combination of intracoronary Abciximab with manual thrombus aspiration & 80 patients received intracoronary Abciximab alone. The primary endpoint was the assessment of myocardial perfusion parameters namely Myocardial Blush Grade (MBG) in the culprit vessel & ST-segment resolution of >70% on ECG at 90 min after PCI. Secondary endpoints were the improvement in LV ejection fraction, cardiovascular mortality & recurrent MI at one-month post-procedure.

Results: Result of the 84 patients who received combination of intracoronary Abciximab with manual thrombus aspiration, the primary endpoints namely the myocardial blush grade (MBG) of 2/3 was achieved in 72 patients (90.74%) & ST-segment resolution of >70% at 90 min was seen in 66 patients (78.57%) ($p<0.001$). Of the 80 patients who received only intracoronary Abciximab without thrombus aspiration, MBG 2/3 was achieved in 38 patients (47.5%) & ST-segment resolution of >70% at 90 min was seen in 28 patients (35%). At one month of follow up the secondary endpoints namely the LVEF in the combination group improved from 43.42±3.73 to 47.88±4.16% ($p=0.12$)and in the Abciximab group improved from 44.78±3.34 to 46.20±3.63%. Recurrent MI was seen in one patient in the combination group ($p<0.001$) & two patients in the ic Abciximab group. There was no cardiovascular mortality noted in the present study ($p<0.001$).

Conclusion: Intracoronary Abciximab + manual thrombus aspiration reduces thrombus burden with better results in microvascular perfusion assessed by ST-segment resolution of >70% at 90 min & higher Myocardial Blush Grade compared to intracoronary Abciximab alone in patients with STEMI undergoing primary PCI.

Keywords: Thrombus aspiration; intracoronary abciximab; percutaneous coronary intervention; STEMI.

1. INTRODUCTION

Timely reperfusion of jeopardized myocardium is the most effective way of restoring left ventricular systolic function and reducing infarct size, thereby reducing the morbidity and mortality associated with ST-elevation myocardial infarction (STEMI) [1]. Microvascular obstruction (MVO) or no-reflow phenomenon refers to a state of poor myocardial perfusion at the microvascular level despite successful restoration of the patency of the epicardial coronary artery [1-3]. Ischemia itself, reperfusion injury, inflammation, or distal embolization of a thrombus and/or plaque debris can cause the development of MVO during the primary percutaneous coronary intervention (PCI) for STEMI [1-5]. Poor myocardial perfusion is associated with a higher occurrence of extensive infarction, left ventricular remodelling and increased mortality than good myocardial perfusion [6-8]. Thus, in the treatment of STEMI, attaining adequate myocardial perfusion is as important as achieving fast epicardial blood flow.

Many studies have assessed the effect of interventional treatments, such as aspiration thrombectomy (AT) [9-13] or glycoprotein (Gp) IIb-IIIa inhibitors, [14-16] on the improvement of myocardial perfusion, which would thereby decrease infarct size in patients with STEMI. It can be hypothesized that combination of Abciximab and AT might synergistically improve myocardial perfusion. Thus far, there are limited data about the benefits of combination treatment with intracoronary (IC) Abciximab and AT as adjuncts to primary PCI for STEMI [16,17]. Therefore, we sought to examine whether a combination of IC Abciximab and AT is superior to IC Abciximab alone in terms of improving myocardial perfusion, as assessed by ST-segment resolution of >70% at 90 min and MBG.

2. MATERIALS AND METHODS

2.1Study Population

All consecutive STEMI patients who were candidates for primary PCI based on the inclusion & exclusion criteria were considered eligible for participation between June 2018 to May 2019.

2.2 Inclusion Criteria

Patients with diagnosis of STEMI as defined by chest pain suggestive for myocardial ischemia for at least 30 minutes before hospital admission, time from onset of symptoms of less than 9 hours, and an ECG with new ST-segment elevation in 2 or more contiguous leads of >0.2 mV in leads V2-V3 and/or >0.1 mV in other leads

or a new-onset left bundle branch block & patients who gave consent for the procedure.

2.3 Exclusion Criteria

Patients with Killip ≥3, pre-procedural Thrombolysis in MI (TIMI) flow grade ≥2 or thrombus grade <2, rescue PCI after thrombolytic therapy, required for emergency coronary artery bypass grafting, presence of cardiogenic shock, known existence of a life-threatening disease with a life expectancy of less than 6 months, inability to provide informed consent, age below 18 years, atrial fibrillation, chronic kidney disease (Cr ≥3 mg/dL), neoplastic disease, platelet count <150000/mL, hemoglobin <10 g/L and contraindications for the use of Abciximab, that include active internal bleeding, history of stroke within 2 years, recent major surgery or intracranial or intraspinal trauma or surgery within 2 months, intracranial neoplasm, arteriovenous malformation or aneurysm, bleeding diathesis, severe uncontrolled hypertension, thrombocytopenia, vasculitis, hypertensive or diabetic retinopathy, severe liver or kidney failure, and hypersensitivity to murine proteins.

2.4 Coronary Angiography and Antithrombotic Regimens

As per the treatment protocol for STEMI patients in the unit, all patients received aspirin (300 mg) and clopidogrel (600 mg) immediately after STEMI diagnosis by electrocardiogram (ECG). After informed consent, patients were taken for primary PCI. An intravenous (IV) bolus injection of unfractionated heparin (70 U/kg) was given and if necessary additional boluses were administered to achieve an activated clotting time of >250 sec. The coronary anatomy was defined and then with a guiding catheter, a 0.014-inch floppy guidewire was passed distal to the lesion. Then thrombus aspiration was done using *Export AP* aspiration catheter (*Medtronic*, *Inc. USA*). Continuous manual suction was performed using a proximal-to-distal approach, which is defined as active aspiration during the initial passage of the lesion. This was followed by a bolus of IC Abciximab (0.25 mg/kg) which was administered via the guiding catheter to ensure high intra thrombus drug concentrations when the distal epicardial coronary flow was visible. An Abciximab infusion after PCI was allowed only for refractory intra-procedural thrombotic complications. Intracoronary vasodilators like nitroglycerin, nitroprusside were used in both groups at the discretion of the primary operator.

In patients who received IC Abciximab alone, a bolus of Abciximab was administered through the guiding catheter proximal to the lesion in the infarct-related artery over 1 minute after the restoration of anterograde flow**.** Stenting of the infarct-related artery was performed in all patients. Decisions regarding direct stenting, the type of stent, and post-stent adjuvant ballooning were at the discretion of the primary operator. Both TIMI flow [18] and myocardial blush [6] were graded on the coronary angiogram as per standard terminology. The duration of cine filming was prolonged by at least three cardiac cycles to make sure that the entire washout phase was included. Myocardial blush grade (MBG) was assessed during the same phase of the cardiac cycle.

After PCI, all patients were treated with aspirin, clopidogrel, beta-blockers, statins & ACEI. The patients were followed up for one month for any cardiovascular mortality, recurrent MI & improvement in LVEF from baseline during admission for primary PCI.

Descriptive statistics were described as means, standard deviations and ranges. For categorical variables, frequencies and percentages were used. Multivariate analysis was carried out wherever appropriate. A value of $p<0.05$ was considered significant and $p<0.001$ was considered highly significant. All tests were performed using SPSS version 16 statistical package with Statistician‘s help.

The study protocol and design were approved by the Institutional Review Board (IRB) of PSG institute of medical sciences and research, Coimbatore.

3. RESULTS

A total of 164 patients with STEMI were eligible for inclusion in the study. 80 patients received intracoronary Abciximab alone. 84 patients received a combination of thrombus aspiration and intracoronary Abciximab.

3.1 Baseline Characteristics

Baseline clinical and laboratory characteristics based on treatment modalities are presented in Table 1. Mean age, male sex, diabetes mellitus history, hypertension, hyperlipidemia, and current

smoking status were balanced between the groups.

The distribution of discharge medication use, including dual antiplatelet therapy, β-blocker, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, or statin, was similar between the 2 groups studied. Ischemic times tended to be shorter in the combination group than in the other group. The frequency of anterior wall MI, Killip classification and left ventricular ejection fraction were balanced between the groups.

3.2 Coronary Angiography and PCI Data

Table 2 depicts the coronary angiography and PCI data. Approximately 67% of the patients underwent primary PCI for a coronary lesion in the left anterior descending artery. Most lesions had TIMI flow grade 0/1 (92.5%), large thrombotic burden (78.5%), were Type-B lesions without significant differences between the groups. All PCI was attempted only for the culprit's vessel. No difference regarding stent number per patient was observed (2 patients in each group had received 2 stents each) and 2 patients in the combination group had the multivessel disease, whereas others had the single-vessel disease. No difference was observed in-stent diameter and the frequency of post-stent adjuvant ballooning among the groups. PCI complications such as distal embolization or dissection were not noted. All patients received either the everolimus or zotarolimus eluting stents.

We compared the myocardial perfusion status (primary endpoints) using following parameters: Final TIMI flow grade, MBG on final coronary angiography and ST-segment resolution of >70% on ECG at 90 min after PCI. Of the 84 patients who received Intracoronary Abciximab + manual thrombus aspiration, final TIMI flow of 3 was achieved in all patients, MBG 2/3 was achieved in 76 patients & ST-segment resolution of >70% at 90 min was seen in 66 patients. Of the 80 patients who received only intracoronary Abciximab without thrombus aspiration, final TIMI flow of 3 was achieved in 56 patients only, MBG 2/3 was achieved in 38 patients & ST-segment resolution of >70% at 90 min was seen in 28 patients. Improved myocardial perfusion parameters were noted in the combination group. The TIMI 3 flow, MBG & ST-segment resolution of >70% at 90 min was found to be statistically significant ($p < 0.001$). On multivariate analysis male sex, frequency of AWMI, Killip class-I, presence of baseline risk factors, shorter ischemic time, baseline LVEF, type of lesion (type-B), higher thrombus grade & TIMI flow(0/1) showed significant primary outcomes in the combination group.

There was no cardiovascular mortality in any group & recurrent MI was seen in two cases in the Abciximab group & 1 patient in the combination group which was unrelated to the target vessel. At one month of follow up (secondary endpoints) the LVEF in the combination group improved from 43.42±3.73 to 47.88±4.16% and in the Abciximab group improved from 44.78±3.34 to 46.20±3.63%. However, the change in LVEF was not found to be statistically significant.

4. DISCUSSION

The main findings of the present study are as follows: A combination of IC Abciximab and thrombus aspiration seemed to be superior to IC Abciximab treatment alone in terms of enhancing myocardial perfusion, as assessed by MBG and ST-segment resolution of >70% on ECG at 90 min after primary PCI for STEMI. Even when TIMI 3 epicardial flow is restored, patients with poor myocardial perfusion have higher mortality than those with good myocardial perfusion.[6] To attain adequate myocardial perfusion in patients with STEMI, prompt and proper revascularization is important. Thrombus aspiration seemed to be beneficial because it can reduce distal atherothrombotic embolism through the retrieval of *in situ* thrombus. Svilaas, et al. [11,13] reported the advantages of manual thrombectomy over conventional PCI in terms of improving MBG as well as reducing the 1-year incidence of MI and cardiac death. Sardella, et al. [12] However, other studies failed to demonstrate the superiority of thrombus aspiration to conventional PCI in the treatment of STEMI [9,10,16]. A meta-analysis by Burzotta et al. showed that manual thrombus aspiration without a distal protection device was better than PCI alone for STEMI patients [17]. Thus, thrombus aspiration is regarded as an important adjunctive tool in the treatment of STEMI, but its routine use is not yet a class I indication in the updated guidelines [19,20]. It can be inferred that the benefit of thrombus aspiration might be enhanced in patients with a shorter ischemic time and heavy thrombotic burden [11,12]. Lesion or clinical-specific studies aimed at revealing the benefits of thrombus aspiration as an adjunct for STEMI is warranted.

Table 1. Baseline characteristics of the two study groups

Variables	Groups		p-value
	IC Abciximab + mechanical thrombus aspiration	IC Abciximab	
Gender			
Male	66(78.57%)	64(80.00%)	<0.001
Female	18(21.42%)	16(20.00%)	0.14^{ns}
Mean Age (yrs)	55.09±11.73	55.85±12.92	0.36^{ns}
Type of MI			
AWMI	60(71.42%)	42(65.00%)	<0.001
IWMI	20(23.80%)	28(35.00%)	0.21^{ns}
PWMI	04(4.760%)	02(2.50%)	0.98^{ns}
Killip class			
Class-I	68(80.95%)	72(90.00%)	<0.001
Class-II	16(19.04%)	08(10.00%)	0.56^{ns}
Risk factors			
a. Smoking			
Yes	58(69.04%)	40(50.00%)	<0.001
b. Hypertension			
Yes	42(50.0%)	46(57.50%)	0.05
c. Hyperlipidemia			
Yes	42(50.0%)	42(52.50%)	0.05
d. T2DM			
Yes	44(52.38%)	42(50.00%)	0.04
Mean window period (hrs)	5.25±1.62	5.38±1.94	0.0001
Ejection fraction%	43.42±3.73	44.78±3.34	0.04

Table 2. Baseline coronary angiographic and procedural parameters

Variables	Groups		p-value
	IC Abciximab + mechanical thrombus aspiration	IC Abciximab	
Target vessel			
LAD	60(71.42%)	52(65.00%)	0.03
RCA	20(23.80%)	26(35.00%)	0.21^{ns}
LCX	04(4.760%)	02(2.50%)	0.98^{ns}
Type of lesion			
A	18(21.42%)	10(12.50%)	0.06^{ns}
B	66(78.41%)	70(87.50%)	0.001
Thrombus grade			
Grade-2	08(9.04%)	18(22.50%)	0.11^{ns}
Grade-3	22(26.19%)	40(50.0%)	<0.001
Grade-4	54(64.28%)	22(27.50%)	<0.001
Mean Stent diameter (mm)	3.07±0.37	2.93±0.28	<0.001
Mean stent length (mm)	24.16±6.44	22.85±5.21	<0.001
TIMI Flow (0/1)	80(95.23%)	72(90.0%)	<0.001

The effect of several medications, such as verapamil, [18] adenosine, [21] nitroprussides, [22] nicorandil, [23] and Gp IIb-IIIa inhibitor, [14-16] on preventing or reducing reperfusion injury has been investigated. However, their efficacy in improving myocardial perfusion was not consistent and remains debatable.

Routine use of a Gp IIb-IIIa inhibitor such as Abciximab is reasonable but is not recommended as class I indication by the current guidelines [19,20]. This might be partially due to the potential increase in bleeding. Instead of a bolus injection followed by continuous infusion of Abciximab, a single bolus administration of Abciximab was proposed to decrease bleeding complications while maintaining anti-ischemic efficacy [15]. It was also suggested that direct IC injection of Abciximab might be superior to its IV injection for improving myocardial perfusion [24-

27]. High local doses of Abciximab may facilitate the dissolution of the antibody to platelets inside the flow-limiting thrombus, thus resulting in the improved dissolution of thrombi and microemboli at the ruptured plaque and further downstream in the microcirculation. A few meta-analyses [26,27] showed that IC Abciximab was more effective in decreasing mortality than IV application. Therfore, the largest randomized Abciximab IC versus IV drug application in the STEMI (AIDA STEMI) trial [40] and another meta-analysis,[29] including the AIDA STEMI trial, showed no difference in mortality between IC and IV Abciximab application. The neutral effect of IC versus IV Abciximab might be due to its subsequent systemic IV infusion. The Intra-coronary Abciximab and Aspiration Thrombec-tomy in Patients With Large Anterior Myocardial Infarction (INFUSE-AMI) trial16 revealed that IC Abciximab via an infusion catheter reduces infarct size. Majority of patients in our study and a majority of patients in the INFUSE-AMI trial [16] had only a bolus of IC Abciximab without subsequent systemic IV infusion. Further studies comparing the efficacy of IC and IV Abciximab bolus application without subsequent infusion are warranted. A study by Sung Gyun Ahn et al. [30], a subgroup analysis of INFUSE-AMI16 and a meta-analysis by Burzotta et al. [17] suggest that a combination of AT (aspiration of thrombus) and Abciximab administration is the most efficient treatment for decreasing infarct size and mortality as compared to Abciximab. These findings are consistent with those in our study. The data collected by Ali et al. [31] compliment the overall INFUSE-AMI trial results. Because the patients who received IC and IV Abciximab combined with aspiration thrombectomy had similar rates of ST-segment resolution and MBG, they concluded that IC instead of IV Abciximab could not enhance myocardial reperfusion in non-selected patients with STEMI undergoing primary PCI, even after aspiration thrombectomy had successfully been performed.

If most thrombotic materials are retrieved by AT, IC Abciximab could further dissolve residual *in situ* thrombus as well as microemboli in the microvasculature. Thus, IC Abciximab application alone without AT might have a limited effect on decreasing a heavy thrombotic burden. There are several methods to assess the adequacy of myocardial perfusion such as TIMI frame count, MBG on coronary angiography,[6] ST-segment elevation recovery on ECG & CMR. Due to cost factors, CMR was not used in the present study. MBG and ST-segment resolution are good predictors of adequate myocardial perfusion [32]. In the present study, MBG and ST-segment resolution of >70% at 90 minutes were used as primary endpoints. Though TIMI-3 flow was achieved in all patients in the combination group, high MBG and ST-segment recovery was not achieved in all patients, as the good epicardial flow does not always translate into good myocardial perfusion [6]. MBG 2/3 and ST-segment recovery in the combination

Table 3. Comparison of myocardial perfusion parameters according to the treatment modalities (Primary endpoints)

Variables	Groups		p-value
	IC Abciximab + mechanical thrombus aspiration	IC Abciximab	
Final TIMI flow grade 3	42(100.%)	28(70.0%)	<0.001
Final myocardial blush grade 2/3	38(90.47%)	19(47.50%)	0.02
ST segment resolution ≥70% at 90 mins	33(78.57%)	14(35.00%)	<0.001

Table 4. Comparison of secondary endpoints at one month

Variables	Groups		p-value
	IC Abciximab + mechanical thrombus aspiration	IC Abciximab	
CVD Mortality	None	None	<0.001
Recurrent MI			
Yes	01(2.38%)	02(5.0%)	0.74^{ns}
No	41(97.61%)	38(95.0%)	<0.001
EF% at one month	47.88±4.16	46.20±3.63	0.12^{ns}

group was found to be statistically significant indicating good myocardial perfusion. The improvement in LVEF at one month from the baseline in the combination group (43.42 ± 3.73 vs 47.88 ± 4.16%; p = 0.12) was not statistically significant compared to that in the group which received Abciximab alone (44.78 ± 3.34 vs 46.20 ± 3.63%; p=0.12). However, a subgroup analysis within the combination group showed that those patients who achieved primary endpoints had improvements in their one-month post PCI LVEF which was statistically significant (43.42 ± 3.73 vs 48.9 ± 3.56; p = 0.05). A similar observation was made by Poli et al. [32]. In their study, however, the LVEF was assessed at 6 months from baseline. It could be conjectured here that LVEF at 6 months from baseline in the present study might show statistically significant improvements though this was not assessed due to feasibility issues. Myocardial stunning could have contributed to a lesser improvement of LVEF at one month in our study. De Luca et al. [33] published a systematic review on the clinical impact of Abciximab in STEMI patients treated with fibrinolysis or primary PCI. In this review, Abciximab reduced both 30-day and long-term (six months to one year) all-cause mortality by 31% and 32%, respectively. No significant increase in major bleeding risks, including intracranial haemorrhage, was noted. Another meta-analysis 37 of 14 randomised trials of IC versus IV glycoprotein IIb/IIIa inhibitors with a total of 3 740 patients undergoing primary PCI showed no statistically significant difference between the IC and the IV groups for the primary outcome of major adverse cardiac events. Subgroup analysis showed however that the IC group was superior to the IV group in short-term major adverse cardiac events rate, TIMI 3 flow, MBG 2 to 3 rates, improvement of LVEF, and ST-segment resolution, compared to the IV group, with a trend towards less stent thrombosis.

Intralesional administration yielded favourable outcomes in terms of myocardial tissue reperfusion as evidenced by the improved Thrombolysis in Myocardial Infarction TIMI flow grade, corrected Thrombolysis in Myocardial Infarction frame count, complete ST-segment resolution and decreased major adverse cardiac events without increasing in-hospital major bleeding events. The IL administration of glycoprotein IIb/IIIa inhibitors can be recommended as the preferred regimen to guard against no-reflow 38.

Bertrand et al. [34] concluded that in patients with ST-elevation myocardial infarction presenting with failed thrombolysis undergoing transradial rescue PCI, IC or IV Abciximab had no significant clinical impact.

There are several limitations to the present study.

First, this is a single-centre study involving a small population. Thus, we could not sufficiently determine clinical and safety endpoints such as mortality and bleeding complications.

Second, the study population was highly selective that is, high-risk patients such as cardiogenic shock patients were excluded while hemodynamically stable subjects, who presented within 9 h of symptom onset and had a large angiographic thrombus burden, were included. Therefore, our findings cannot be extrapolated to all STEMI patients undergoing primary PCI.

Third, the LVEF was assessed at 1 month and myocardial stunning may have contributed to non-achievement of the secondary end point. Hence, a longer follow-up period is necessary.

Finally, we did not use an IC infusion catheter to deliver Abciximab. Therefore, the drug might have leaked into the aorta or the subtending coronary vessel, resulting in inefficient delivery to the plaque rupture site and corresponding myocardium.

To our knowledge, this is the first Indian study addressing the use of a combination of thrombus aspiration with intracoronary Abciximab. There are several inherent confounding factors which influence the decision of primary PCI in a patient with AMI in developing countries. Cost of therapy and affordability is probably the most important factor. The additional cost for thrombus aspiration needs to be considered against the additional advantages in terms of better clinical outcome. The strength of this study lies in analyzing current prevailing practice in a tertiary care cardiology centre in a developing country where an informed decision is made by patients regarding their treatment after consideration of benefits and cost of interventions.

5. CONCLUSION

Thrombus aspiration followed by a bolus of IC Abciximab may be an efficient adjunctive

combination therapy to enhance myocardial perfusion in patients with STEMI undergoing primary PCI who present with a mean window period of 5.25±1.62 hrs and have a large angiographic thrombotic burden. A randomized, controlled trial powered for clinical and safety endpoints is required to confirm the benefits of combination treatment using IC Abciximab and thrombus aspiration in patients presenting with STEMI.

CONSENT

As per international standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard, ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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