ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Role of intracoronary adenosine on prevention of no reflow during Primary PCI in STEMI patients guided by MVO in CMR

Ahmed Hatata[1] ,Wael EL-Kilany[2] , Ahmed Rezk[3] , Tarek Zaki[4]

[1] Assistant lecturer of cardiology Ain shams University , Egypt

[2] Professor of cardiology Ain shams University , Egypt

[3]Lecturer of cardiology Ain shams University, Egypt

[4] Professor of cardiology Ain shams University, Egypt

Corresponding Author: Ahmed Ibrahim Hatata

Abstract:

Background: Microvascular obstruction (MO) or no-reflow phenomenon is an established complication of coronary reperfusion therapy for acute myocardial infarction. It is increasingly recognized as a poor prognostic indicator and marker of subsequent adverse LV remodeling. Microvascular obstruction (MO) or no-reflow phenomenon is an established complication of coronary reperfusion therapy for acute myocardial infarction. It is increasingly recognized as a poor prognostic indicator and marker of subsequent adverse LV remodeling.

Results: There was no significant difference between two groups regarding TIMI and MBG score .There was a significant difference in myocardial salvage index and myocardium at risk with p value less than 0.001 . Yet no increase in myocardial hemorrhage among the two groups . There was significant improvement in EF , LV mass and LV volumes in those who were given adenosine .

Conclusion: Adenosine improves no reflow on giving as a prophylactic drug . It improves the microcirculation thus increasing the salvaged myocardium improving micro vascular obstruction and does not increase the percentage of microvascular hemorrhage.

Keywords:STEMI, Coronary no-reflow, MVO , MV HGE , Salvage Index, TIMI , MBG adenosine.

Background: Microvascular obstruction (MO) or no-reflow phenomenon is an established complication of coronary reperfusion therapy for acute myocardial infarction. It is increasingly recognized as a poor prognostic indicator and marker of subsequent adverse LV remodeling. Although MO can be assessed using various imaging modalities including electrocardiography, myocardial contrast echocardiography, nuclear scintigraphy, and coronary angiography, evaluation by cardiovascular magnetic resonance (CMR) is particularly useful in enhancing its detection, diagnosis, and quantification, as well as following its subsequent effects on infarct evolution and healing. The contribution of microvascular injury in causing anatomic myocardial "no-reflow" was first described in the 1970's[1, 2, 3].

CMR techniques for microvascular obstruction:

The advent of fast CMR techniques in the 1990's facilitated the study of the temporal perfusion patterns within acute perfused infarcts following bolus administration of gadolinium by allowing a temporal resolution of seconds rather than minutes[4, 5, 6] .

Time course of MO post-infarction:

MO extent varies as a function of time from the acute ischemic event. Experimentally, it has been demonstrated that there is an expansion of the anatomic no-reflow area by thioflavin-S in the hours following reperfusion, with a tripling in size between 2 min and 2–4 h and a further smaller increase up to 8 h following reperfusion[7, 8, 9]. Following an initial hyperemic phase within the first 2 min of reperfusion, there is a marked, progressive decline in myocardial blood flow which plateaus at around 50% of normal flow, which supports these findings.

MO and infarct hemorrhage:

As part of the disruption to the microvasculature observed upon reperfusion, large gaps can be seen in the endothelial wall that cause extravasation of red blood cells, i.e. hemorrhage. In experimental models performed as early as the 1980's, it was observed that any hemorrhage was limited to the region of severe microvascular injury,.lagged behind the no-reflow process and its extent was directly proportional to the duration and severity of the preceding ischemia (with the severity of ischemia determined predominantly by collateral flow)[8].

Hemorrhage can be assessed using T2-weighted and T2* imaging. The appearance of hemorrhage on MRI is

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

based upon the paramagnetic effects of hemoglobin degradation products. Initially, hemorrhage may consist of oxyhemoglobin which lacks paramagnetic effects. Subsequently, probably within the first few days after acute MI, oxyhemoglobin denatures into deoxyhemoglobin which does exert paramagnetic effects and will significantly reduce the T2 time. Deoxyhemoglobin is then gradually converted over the following few days into methemoglobin, which is strongly paramagnetic with respect to both T1- and T2-weighted sequences. After ~2 weeks, methemoglobin is converted into hemosiderin which is contained within macrophages and also results in low T2 values. Hence, acutely post-MI, hemorrhage can be visualized on CMR as hypo enhanced regions surrounded by elevated signal intensity representing myocardial edema on T2-weighted imaging and most studies show that hemorrhage is limited to those patients with evidence of MO[10].

Methods:

Study design:

This is an interventional prospective pilot study which was conducted on patients presenting to cardiology department in Ain Shams University hospitals with STEMI (St segment elevation myocardial infarction in the first 12 hours of presentation.) DEFINED as elevation of cardiac troponins at least one value above 99th percentile in a clinical setting consistent with myocardial ischemia.

Sample size: 50 patients.

Inclusion criteria:

1. Patients presented with STEMI for primary PCI.
2. Patients with TIMI I flow after establishing flow by PTCA wire or PTCA balloon or by thrombus aspiration.
3. Coronary angiography shows total occluded vessel with TIMI zero flow
4. Thrombus burden grade five
5. Informed consent about adenosine is taken before procedure and hazards of adenosine are discussed with the patient and operator according to protocol

Exclusion criteria:

1) Lack of informed consent
2) Patients presented with cardiogenic shock
3) Patients with complete heart block or second degree heart block.
4) Patient with CKD on dialysis
5) Previous myocardial infarction , CABG
6) ICM with low ejection fraction less than 35 %
7) Evidence of previous ischemia (previous CA with significant CAD lesion more than 70 % by coronary angiography or by IVUS or FFR)

Methodology:

All patients who were qualified for the study on the basis of the inclusion and exclusion criteria undergone the following:

1. Clinical evaluation including:

Thorough history taking Personal history: Age, smoking, alcohol.

Present history: assessment of chest pain and functional capacity.

Past history: Ischemia: Previous ischemic events, whether chest pain had started before infarction (pre-infarction angina) or not.

Medical: Diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, peripheral vascular disease, cerebrovascular disease and obesity.

2. Family history: family history of premature coronary artery disease CAD.

3. Clinical examination:

General examination: with special emphasis on ABP, heart rate.

Local cardiac examination

Procedures:

- Patients had been randomized into two groups the Group: A were given adenosine routinely after establishing TIMI I flow either spontaneously or by passing the wire or non-inflated balloon which is defined as : Faint antegrade coronary flow beyond the occlusion, with incomplete filling of the distal coronary bed.

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Adenosine had been given through catheter to the distal coronary bed by loading bolus 1 mg and dose can be repeated after 15-20 mins up to 2mg to LAD and 1 mg in RCA and the remainder of PCI protocol will be done according to operator decision.

While the group B had not been given adenosine, MRI was done within 48 hrs. of primary PCI and repeated for follow up after three months.

In the MRI protocol, with the assessment of:

1. MVO and degree of hemorrhage within MVO
2. Tissue edema.
3. Ejection fraction, degree of mitral regurgitation
4. Segmental wall motion abnormalities.
5. Extent infarction whether transmural or sub endocardial and degree of fibrosis.

Statistical analysis:

Data had been collected, verified, revised and then edited on PC.

Categorical variables had been expressed as their absolute and relative frequencies (percentage), while continuous variables had been presented as mean values ± standard deviation.

Statistical analysis had been performed using SPSS statistical package.

Differences had been considered statistically significant at a p value <0.05 level and highly significant at a p value < 0.001.

Results:

-**Table one** shows demographic data of the study with average 57 years with total number of 50 patients with seven times males than females .

Many risk factors were included in the study as DM , HTN and Dyslipidemia . All the patients involved were smokers.

		Total no. = 50
Age (years)	Mean ± SD	57.40 ± 8.12
	Range	30 – 76
Sex	Female	6 (12.0%)
	Male	44 (88.0%)
Risk factors	DM	50 (100.0%)
	HTN	50 (100.0%)
	Smokers	50 (100.0%)
	Dyslipidemia	2 (4.0%)
	FH	2 (4.0%)
	Rheumatoid	2 (4.0%)
	HCV	1 (2.0%)

-**Table two** shows target vessels , MBG and TIMI score among the whole study showing thirty two patients with infarction within LAD territory and more than 40 patients with TIMI score more than one , while more than thirty patients with MBG more than one .

		Total no. = 50
Target vessel	LAD	32 (64.0%)
	RCA	7 (14.0%)
	LCX	8 (16.0%)
	OM	3 (6.0%)
	LM	1 (2.0%)
	Ramus	1 (2.0%)
	D2	1 (2.0%)
TIMI flow	I	1 (2.0%)
	II	9 (18.0%)
	III	40 (80.0%)

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MBG	0	1 (2.0%)
	II	17 (34.0%)
	III	32 (64.0%)

Table three shows the target vessels between two groups : IRA was within LAD in 16 patient in both groups equally distributed and all of them were proximal LAD (before 1st Diagonal)
22 patients with TIMI III flow in group A while less cases in group B also shows variation in MBG among two groups with 17 cases 68% in grp with MBG III and 15 cases 60 % in group B statistically not significant.

		Group A	Group B	P-value
		No. = 25	No. = 25	
Target vessel	LAD	16 (64.0%)	16 (64.0%)	1.000
	RCA	3 (12.0%)	4 (16.0%)	0.684
	LCX	4 (16.0%)	4 (16.0%)	1.000
	OM	2 (8.0%)	1 (4.0%)	0.552
	LM	1 (4.0%)	0 (0.0%)	0.312
	Ramus	1 (4.0%)	0 (0.0%)	0.312
	D2	1 (4.0%)	0 (0.0%)	0.312
TIMI flow	I	1 (4.0%)	0 (0.0%)	0.124
	II	2 (8.0%)	7 (28.0%)	
	III	22 (88.0%)	18 (72.0%)	
MBG	0	1 (4.0%)	0 (0.0%)	0.437
	II	7 (28.0%)	10 (40.0%)	
	III	17 (68.0%)	15 (60.0%)	

Table three shows the base line MVO at the first visit and after three months .
Shows also MV hemorrhage at the base line and after three months one patient in each grp has microvascular hemorrhage .
Salvage index is much more significant in group A (adenosine group), With significant salvaged myocardium

		Group A	Group B	P-value
		No. = 25	No. = 25	
MVO baseline	No	15 (60.0%)	0 (0.0%)	0.000
	Yes	10 (40.0%)	25 (100.0%)	
MVO after 3 months	No	24 (96.0%)	25 (100.0%)	0.312
	Yes	1 (4.0%)	0 (0.0%)	
MV HG baseline	No	24 (96.0%)	24 (96.0%)	1.000
	Yes	1 (4.0%)	1 (4.0%)	
MV HG after 3 months	No	24 (96.0%)	24 (96.0%)	1.000
	Yes	1 (4.0%)	1 (4.0%)	
Myocardial salvage index	Mean ±SD	65.40 ± 8.41	33.80 ± 9.92	0.000
	Range	50 – 80	20 - 50	

		Group A	Group B	P-value
		No. = 25	No. = 25	
LVEDV	Mean ± SD	114.80 ± 20.60	94.00 ± 29.28	0.006
	Range	89 – 179	13 – 156	
LVESV	Mean ± SD	67.60 ± 23.57	53.36 ± 22.46	0.034
	Range	30 – 135	20 – 100	
Tissue Edema at visit one	No	0 (0.0%)	0 (0.0%)	NA
	Yes	25 (100.0%)	25 (100.0%)	

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EF improvement between two visits	No Yes	2 (8.0%) 23 (92.0%)	6 (24.0%) 19 (76.0%)	0.123
LV mass	Mean ± SD Range	131.12 ± 15.75 99 – 172	144.48 ± 30.61 86 – 217	0.058
SV 1	Mean ± SD Range	48.88 ± 16.05 20 – 85	36.88 ± 12.15 21 – 70	0.005
SV 2	Mean ± SD Range	52.76 ± 18.07 14 – 88	41.84 ± 10.55 23 – 72	0.012
Myocardial salvage index	Mean±SD Range	65.40 ± 8.41 50 – 80	33.80 ± 9.92 20 - 50	0.000

Table four shows mean average LV end diastolic diameter and end systolic diameter . There are a significant values in group A than group B in end diastolic diameters and stroke volumes .

Improvement in EF between two visits which shows statistically non-significant and there is a significant salvaged myocardium towards adenosine group .

Discussion:

This study was conducted on fifty patients presented to Ain- shams University by ST segment elevation myocardial infarction in the early twelve hours of pain .

The study is an interventional pilot , comparing two groups: one was given adenosine and the other group not aiming for assessment of MVO and MV hemorrhage and calculating myocardial salvage index for both groups .

In this study we compare adenosine which is a drug used in treatment of no reflow , here we used it in prevention of no reflow and comparing the outcome with control group.

The main pros and cons of intracoronary agents. Here we mean adenosine that many of them increase the distal flow also increase myocardial capillary leakage and tissue destruction and hence the composite data for the outcome may be reversed.

Many studies showed the effects of these agents and how to measure their success and hence the success of reperfusion .

Adenosine although increase blood flow distally also increase the risk for hemorrhage and tissue loss we here in this study showed that the adenosine affect the outcome by decreasing MVO without increasing the hemorrhage percentage .

There was no difference in myocardial hemorrhage among two groups yet the small sample size may contribute to that.

Yet there was no statistically difference in improving TIMI flow or MBG grade.

Conclusion:

Adenosine improves no reflow on giving as a prophylactic drug . It improves the microcirculation thus increasing the salvaged myocardium improving micro vascular obstruction and does not increase the percentage of microvascular hemorrhage.

Study Limitation:

1- Small sample size .

2- Single center study .

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3- COVID era and poor compliance of the patients to come to hospital to do investigation and to repeat the investigation.

4- In ability to use adenosine in cardiogenic shock patients who have more sluggish circulation and no reflow .

5- The availability of adenosine in the market .

6- Short duration follow up .

7-Lack of clinical follow up and mortality and recurrent hospital admissions to the patient

List of abbreviation:
MBG : myocardial blush grade .
TIMI :Timi flow score system
MVO : microvascular obstruction .
CMR : cardiac magnetic resonance .
STEMI : St segment myocardial infarction .
MV HG : microvascular hemorrhage .
SV : stroke volume .
LV : left ventricle .
EF : ejection faction .
LVEDV : left ventricular end diastolic volume .
LVESV : left ventricular end systolic volume .

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