Al-Azhar Med. J. *Vol. 49(3), July, 2020, 1101-1112*
DOI : 10.12816/amj.2020.91632
https://amj.journals.ekb.eg/article_91632.html

IMPACT OF INTRACORONARY ADENOSINE ADMINISTRATION DURING PRIMARY PERCUTANEOUS CORONARY INTERVENTION

By

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ABSTRACT

Background: Currently myocardial reperfusion with p-PCI is the best treatment strategy for STEMI, However, myocardial perfusion at the cellular level remains impaired despite removal of coronary obstruction in up to 50% of STEMI patients Several methods have been evaluated to improve reperfusion, including heart rate reduction, aspiration thrombectomy and several pharmacological approaches, such as glycoprotein platelet inhibitors, adenosine and drugs able to dilate the microcirculation, seem to be most effective when locally delivered through IC injection, probably because this results in an increased drug bioavailability in the area at risk.

Objective: the aim of our study was to clarify the efficacy of IC adenosine versus standard therapy only in STEMI patients undergoing p-PCI.

Patients and methods: Selected 45 patients presented to emergency room by acute STEMI and were randomized into two groups: Control group (25 patients) and Patient group who received IC adenosine (20 patients). Both were evaluated during p-PCI by MBG and TIMI flow grade, after the procedure, both groups was evaluated by STR in ECG, cardiac enzymes at 0-6-12 hours, and echocardiography within 24 hours and after 40 days.

Results: in patient group, TIMI flow was significantly better, incidence of ST resolution was significantly higher, and level of cardiac enzymes was significantly higher at 6 hours and significantly lower at 12 hours. Moreover, we found a larger increase in LVEF - and subsequently reduction in the incidence of heart failure, more improvement of MR, TR, PASP and TAPSE in patient group.

Conclusion: This study clarified clinical benefits for IC adenosine in hard endpoints, such as TIMI flow, percentage of LVEF improvement, in patients undergoing p-PCI.

Key words: Adenosine, p-PCI, myocardial perfusion.

ABBREVIATIONS

BMI: body mass index - FMC: first medical contact – IC: intracoronary – IRA: infarct related artery - MBG: myocardial blush grade – MR: mitral regurgitation - MW: Mann-Whitney Test - PASP: Pulmonary artery systolic pressure- p-PCI: primary percutaneous coronary intervention – STEMI: ST- segment elevation myocardial infarction – STR: ST segment resolution – TAPSE: Tricuspid annular plane systolic excursion – TIMI: thrombolysis in myocardial infarction – TR: tricuspid regurgitation.

INTRODUCTION

Currently myocardial reperfusion with p-PCI is the best treatment strategy for STEMI *(O'Gara et al., 2013)*. However, myocardial perfusion at the cellular level remains impaired despite removal of coronary obstruction in up to 50% of STEMI patients, the current factors, embolization of coronary thrombus into the distal vasculature, micro vascular plugging, vasospasm, interstitial edema, local inflammation, and cellular injury play a role *(Niccoli et al., 2009)*. Several methods have been evaluated to improve reperfusion, including heart rate reduction, aspiration thrombectomy and several pharmacological approaches, such as glycoprotein platelet inhibitors, adenosine and drugs able to dilate the microcirculation *(De Rosa et al., 2014)*. These pharmacologic approaches seem to be most effective when locally delivered through IC injection, probably because this results in an increased drug bioavailability in the area at risk *(Zhao, et al., 2014)*. Endogenous adenosine plays an important role in maintaining myocardial perfusion through its potent vasodilator effect and NO-inducing proprieties, as well as its anti-inflammatory and anti-platelet properties. Interestingly, *Bune et al. (2015)* have recently shown in an animal model that administration of ADP- that is largely converted to adenosine by endothelial cells in the blood stream- is indeed able to substantially limit the final infarct size and that this effect is at least in part related to an increased release of t-PA. The use of adenosine in patients with STEMI has been tested in previous studies, but results are conflicting because of small sample sizes, different dosages or administration routes *(Singh,et al. 2012)*.

The aim of the present study was to clarify the effect of IC adenosine versus placebo on clinical outcomes in patients with STEMI undergoing p-PCI.

PATIENTS AND METHODS

Our study includes 45 patients presented by acute STEMI divided into two groups Patients group include 20 patients who received IC Adenosine, while Control group include 25 patients who received the standard therapy. The following patients were excluded: if thrombolytic therapy was given, with previous history of CAD, Previous heart failure, Congenital heart diseases, cardiac surgery, permanent AF, if receiving oral anticoagulation, Allergy to Adenosine, or if patients with poor Echocardiographic window.

All patients were subjected to Informed consent, Complete history as regard risk factors, Heart failure symptoms, Drug history, Full physical examination ,Blood sample for CBC especially hemoglobin level, serum creatinine, RBS, INR, LDL, HDL, Triglyceride, resting 12 leads ECG within 10 minutes from FMC and after 90 minutes from p-PCI to assess the STR %, p-PCI within 90 minutes from FMC with & Without adenosine Pretreatment, Patients who were randomized to the adenosine group received (100 mic in case of left system CAD, and 50 mic in case of RCA occlusion) of adenosine (diluted into 5 mL of normal saline) through the guiding catheter into the culprit coronary artery after aspiration of the present thrombi (if applicable) and prior to stenting. The rest of the intervention strategy, including use of glycoprotein IIb/ IIIa inhibitors and drug-eluting stents, were done once indicated. Patients who

were randomized to the standard therapy did not received adenosine pretreatment, and the procedure was carried out in the usual manner. Administration of adenosine for treatment of no-reflow phenomenon during the procedure was allowed in both groups. Estimation of the perfusion degree were done by TIMI flow grade and myocardial Blush grade (MBG).All patients received a Clopidogrel Tablet 600 mg PO, ASA 300mg PO & Enoxaparin 1mg/kg at FMC. Post-procedural antiplatelet regimen consisted of aspirin 81mg p.o /day indefinitely and Clopidogrel 150 mg p.o/day for 7-14 day then 75 mg PO daily for one year. Full study Transthoracic Echocardiography (TTE) was performed immediate after p-PCI within 24 hours and another study was done after 40 days apart from the procedure, especially for assessment of the LV EF %, Grade of MR,TR,–if present-TAPSE and PASP.

Statistical analysis:

Data were analyzed using Statistical Program for Social Science (SPSS) version 24. Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Mean (average): is the central value of a discrete set of numbers, specifically the sum of values divided by the number of values. Standard deviation (SD): is the measure of dispersion of a set of values, a low SD indicates that the values tend to be close to the mean of the set, while a high SD indicate that the values are spread out over a wider range. Median is the value separating the higher half from the lower half of data. The basic advantage of median comparing to mean is that the median is not skewed so much by small proportion of extremely large or small values. IQR is the measure of statistical dispersion, being equal to the difference between 75th and 25th percentile. The following tests were done: Independent-samples t-test of significance: was used when comparing between two means. Mann –Whitney U test: was used when comparing between two means (for abnormal distributed data). Chi-square test: was used when comparing between non-parametric data. Probability (P-value): P-value < 0.05 was considered significant.

RESULTS

- The following tables represent comparison between patient and control groups:
- There was no statistical significant difference (p-value > 0.05) between studied groups as regard risk factors (age, sex, DM, HTN, dyslipidemia, smoking, family history and BMI) **(Table 1)**.

Table (1): Comparison between studied groups as regard demographic criteria and risk factors

Risk factors \ Groups		Patients (N = 20)		Control (N = 25)		P-value
Age	Mean ± SD	56.9 ± 8.5		55.6 ± 11.5		0.678
Sex	M	16	80 %	23	92 %	0.239
	F	4	20 %	2	8 %	
DM	No	11	55 %	19	76 %	0.138
	Yes	9	45 %	6	24 %	
HTN	No	11	55 %	14	56 %	0.947
	Yes	9	45 %	11	44 %	
Dyslipidemia	No	12	60 %	8	32 %	0.06
	Yes	8	40 %	17	68 %	
Smoking	No	9	45 %	8	32 %	0.371
	Yes	11	55 %	17	68 %	
Family history	No	18	90 %	25	100 %	0.106
	Yes	2	10 %	0	0 %	
BMI	Mean ± SD	29.1 ± 4.6		28.9 ± 4.1		> 0.05

- Catheterization data of both groups as regard type of STEMI presentation, IRA, single versus multi vessel disease and complete versus staged PCI **(Table 2)**.

Table (2): Description of catheterization data in both groups

Catheterization data \ Groups		Control group (N = 25)		Patients group (N = 20)	
Presentation type Of STEMI	Anterior	12	48%	10	50%
	Antero- Lateral	1	4%	0	0%
	Antero- inferior	0	0%	1	5%
	Inferior	7	28%	5	25%
	Infero -Posterior	3	12%	1	5%
	Infero -Lateral	1	4%	0	0%
	Postero-Lateral	1	4%	0	0%
	Lateral	0	0%	2	10%
	Posterior	0	0%	1	5%
IRA	LAD	12	48%	11	55%
	LCX	3	12%	2	10%
	OM	2	8%	1	5%
	RCA	8	32%	6	30%
Single vessel disease		12	48%	8	40%
Multi vessel disease		13	52%	12	60%
Complete revascularization	No	15	60%	12	60%
	Yes	10	40%	8	40%
Staged PCI	No	21	84%	14	70%
	Yes	4	16%	6	30%

- There was statistically significant difference (p-value < 0.05) between studied groups as regard TIMI flow but no statistical significant difference (p-value > 0.05) between both studied groups as regard MBG also there was no cases with no-reflow **(Table 3)**.

Table (3): Comparison between studied groups as regard TIMI flow, MBG and no reflow

Reperfusion parameter \ Groups		Patients (N = 20)		Control (N = 25)		P-value
TIMI flow	II	0	0%	9	36%	0.003
	III	20	100%	16	64%	
MBG	II	2	10%	6	24%	0.222
	III	18	90%	19	76%	
No reflow	No	20	100%	25	100%	-
	Yes	0	0%	0	0%	

- There was statistically significant difference between studied groups as regard % of STR(ST segment resolution) in ECG, Hs Troponin T level (after 6 hours and after 12 hours) (P value <0.05) but no statistical significant difference between studied groups as regard Hs Troponin T level at 0 hours, or CKMB at 0,6,12 hours (p-value > 0.05) **(Table 4)**.

Table (4): Comparison between studied groups as regard STR%, Hs Troponin T, and CKMB levels

Cardiac enzymes \ Groups			Patients (N = 20)	Control (N = 25)	P-value
STR%		Median	75%	62%	0.001
		IQR	18.5(68.5 – 87)	17 (50 – 67)	
Hs Troponin T	0 hour	Median	47	47	0.918 NS
		IQR	896.5 (29 – 925.5)	1363 (26 – 1389.5)	
	6 hours	Median	6492	4829	0.028
		IQR	4864.5 (4906– 9770.5)	4937 (2436.5– 7373.5)	
	12 hours	Median	1594	3111	0.01
		IQR	1970 (574.5 – 2445)	6535 (1600.5– 8135.5)	
CK-MB	0 hour	Median	5	5	0.801
		IQR	44.25 (3.25 – 47.5)	43.5 (3 – 46.5)	
	6 hours	Median	300	132	0.058
		IQR	197.5 (102.5 – 300)	264 (36 – 300)	
	12 hours	Median	50	93	0.102
		IQR	56.75 (18.25 – 75)	170 (29.5 – 199.5)	

- There was statistically significant difference (p-value < 0.05) between studied groups as regard MR, TAPSE & TR ,but no statistical significant difference (p-value > 0.05) between studied groups as regard EF and PASP (within 24 hour) **(Table 5)**.

Table (5): Comparison between studied groups as regard TTE (within 24 hours)

TTE \ Groups		Patients (N = 20)		Control (N = 25)		Test	P-value
EF	Mean	44.8		41.3		0.95	0.346
	±SD	12.8		11.8			
MR	No MR	8	40%	11	44%	X^2 = 12.1	0.007
	grade I	7	35%	7	28%		
	grade II	5	25%	0	0%		
	grade III	0	0%	7	28%		
TR	No TR	14	70%	12	48%	X^2 = 7.6	0.023
	grade I	5	25%	3	12%		
	grade II	1	5%	10	40%		
TAPSE	Normal	18	90%	11	44%	X^2 = 10.3	0.001
	Impaired	2	10%	14	56%		
PASP	Median	24		27		MW= 195	0.207
	IQR	7.75 (22.25 – 30)		6 (25 – 31)			

- There was statistically significant difference (p-value < 0.05) between studied groups as regard LVEF%, MR, TR, TAPSE & PASP (after 40 days follow up) **(Table 6)**.

Table (6): Comparison between studied groups as regard TTE (after 40 days)

TTE \ Groups		Patients (N = 20)		Control (N = 25)		P-value
EF	Mean	53.5		43.5		0.006
	±SD	10.2		12.4		
MR	No MR	16	80%	11	44%	0.041
	Grade I	2	10%	7	28%	
	Grade II	2	10%	2	8%	
	Grade III	0	0%	5	20%	
TR	No TR	17	85%	14	56%	0.011
	Grade I	3	15%	2	8%	
	Grade II	0	0%	9	36%	
TAPSE	Normal	19	95%	13	52%	0.002
	Impaired	1	5%	12	48%	
PASP	Median	23.5		26		0.015
	IOR	4.25 (22.25-26.5)		7.5 (25– 32.5)		

- There was no statistical significant difference (p-value > 0.05) between studied groups as regard MACE **(Table 7)**.

Table (7): Comparison between studied groups as regard peri-procedural MACE

MACE \ Groups	Control (N = 25)			Patient (N=20)			P-value
NO MACE	21	84%		18	90%		0.05%
Survived from VF	1	4%	16%	1	5%	10%	
pulmonary edema	2	8%		0	0%		
AF	1	4%		0	0%		
Advanved transient AV block	0	0%		1	5%		

DISCUSSION

The main findings of our study are that IC Adenosine: a) is effective in improving myocardial reperfusion and TIMI flow in STEMI patients undergoing p-PCI; b) favors a better left and right ventricular remodeling, as suggested by the significantly higher LVEF and TAPSE value and subsequently the lower incidence of heart failure, also better improvement in MR, TR & PASP in the adenosine group; c) no statistically significant difference in the incidence of no reflow nor per procedural MACE. The clinical benefit observed with IC adenosine largely outweighs the increased incidence of transient atrio-ventricular block. Despite the "no reflow" is associated with a poor prognosis results from previous studies are conflicting and inconclusive. Several studies have investigated the benefits of the preventive use of adenosine during and after reperfusion therapy for acute myocardial infarction. These studies used different, sometimes complicated and time-consuming, protocols of adenosine infusion during and after the PCI procedure or thrombolytic therapy.

Akturk et al. (2014) showed that IC Verapamil provides better TIMI flow in comparison with IC adenosine, so in this study they did not ignore the clinical benefits of IC adenosine despite better results of IC Verapamil which was beyond the scope of our study.

Mukesh et al. (2012) analyzed 7 studies involving 1030 participants who were treated with IC adenosine. They assessed mortality, heart failure, MACE, STR, LVEF %, TIMI flow, MBG, and side effects, but were unable to draw definitive conclusions on any of the clinical outcomes. Their meta-analysis included one study used a nonplacebo (nitroglycerine) control group.

Polimeni et al. (2014) reported a meta-analysis of conference abstracts, which included 10 RCTs in which patients were treated with IC adenosine. They found that adenosine treatment improved major cardiovascular adverse events and heart failure rates in patients with STEMI treated with PCI. Their findings are partly consistent with our conclusions.

Stoel et al. (2008) investigated the influence of very-high-dose intracoronary adenosine (60 mg within 5 to 10 minutes) on persistent ST-segment elevation after primary PCI. Intracoronary adenosine accelerated ST segment resolution and recovery of micro vascular perfusion, as assessed by the TIMI frame count and MBG.

These results should not be misunderstood, and the golden STEMI rule "earlier is better" holds true for IC adenosine as for all other STEMI treatments. As for any study, some limitations should be acknowledged that are related to :1) different definitions in the studies for different endpoints ;2) some differences in the baseline characteristics found between the studies; 3) dose and method of adenosine administration were heterogeneous among the previous studies; 4) difficult patient compliance in the follow up period 5) given that our study and previous studies were designed on a relatively limited number of included patients , for this reason all results on hard clinical endpoints should be interpreted with caution. Further studies are needed to

establish a cut-off to identify the optimal dose to be administered. Finally, the interaction between adenosine and concomitant treatments, such as antiplatelet agents, also deserves further attention.

CONCLUSION

Our study provides evidence that, besides increasing the reperfusion indices, IC adenosine is associated to a more favorable left ventricular remodeling, with larger increase in LVEF and lower incidence of heart failure and also can be given safely as an IC route.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

ACKNOWLEDGMENTS

Thanks to Dr Abdelmaksoud Ahmed, Dr. Hani Khalaf and Dr. Elsayed Elmerghany, Faculty of Medicine, Al Azhar University, Cairo,Egypt- Dr. Ahmed Bakry, Faculty of Medicine, South Valley University, Qena, Egypt– Dr. Ahmed Daod, Dr-Erfan & Bagedo general Hospital, Jeddah, KSA, for their great efforts during doing this study.

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تأثير حقن الشريان التاجى بعقار الادينوسين اثناء اجراء دعامة اولية فى مرضى احتشاء عضلة القلب الحاد

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خلفية البحث: يعد إعادة تروية عضلة القلب عن طريق فتح الشريان المسبب لإحتشاء عضلة القلب بإستخدام القسطرة التداخلية هو العلاج الأمثل في علاج إحتشاء عضلة القلب المصاحب بإرتفاع مقطع إس تي في تخطيط القلب ومع هذا مازال هناك قصور فى إعادة تروية عضلة القلب علي مستوي خلايا أنسجة عضلة القلب بالرغم من إزالة مسبب إنسداد الشريان التاجي في ما يقرب من 50% من عدد الحالات.

الهدف من البحث: دراسة تأثير حقن الشرايين التاجية للقلب بعقار الأدينوزين أثناء إجراء قسطرة تداخلية أولية فى مرضى إحتشاء عضلة القلب الحاد المصاحب لإرتفاع مقطع إس تي.

المرضى وطرق البحث: قيمت الدراسة 45 مريضا يعانون من إحتشاء عضلة القلب الحاد المصاحب لإرتفاع مقطع إس تي. وبعد موافقتهم للدخول فى هذه الدراسة وإكتمال كل المعايير الأخلاقية الطبية تم تقسيمهم لمجموعتين: مجموعة المرضي وعددهم 20 مريضا والذين تم حقنهم بعقار الأدينوزين ومجموعة التحكم وعددهم 25 مريضا وكانت تتراوح بين 18 و 75 عام.

قبل إجراء القسطرة التداخلية فإن جميع المرضى تم إعطاؤهم أسبرين 300 مجم- وكلوبيدوجرل 600 مجم عن طريق الفم وإنوكسابارين 1 مجم/ كجم تحت الجلد. وقد تم عمل تخطيط قلب فى خلال 10 دقائق من أول مقابلة طبية للمريض وتخطيط قلب أخر بعد الإنتهاء من القسطرة التداخلية ب 90 دقيقة.

وتم إدخال جميع المرضي معمل القسطرة فورا وإخضاعهم للعلاج المتبع طبقا للتوصيات والإرشادات العالمية.

وقد تم حقن مجموعة المرضي محل الدراسة بعقار الأدينوزين داخل الشريان التاجي المصاحب للإحتشاء وذلك فور وجود أي نسبة تدفق للدم في الشريان وقبل وضع الدعامة داخل الشريان –إذا استدعي الامر- وذلك عن طريق القسطرة المرشدة على مدار 3- 5 دقائق بجرعة مقدارها 100 ميكرو جرام إذا كان الشريان التاجي الأيسر هو المصاحب للإحتشاء وبجرعة 50 ميكرو جرام إذا كان الشريان التاجي الأيمن هو المصاحب للإحتشاء.

كما تمت مراقبة إنزيمات القلب (تروبونين تي عالي الحساسية و CK MB)على مدار 0-6-12 ساعة من أول مقابلة طبية.

تم عمل موجات فوق صوتية علي القلب في غضون 24 ساعة من إجراء القسطرة التداخلية وأيضا بعد 40 يوم من حدوث إحتشاء عضلة القلب.

نتائج البحث: إعطاء عقار الأدينوزين داخل الشريان التاجي المصاحب لإحتشاء عضلة القلب الحاد اثناء إجراء قسطرة تداخلية أولية في مرضى إحتشاء عضلة القلب المصاحب لإرتفاع مقطع إس تي مفيد للمرضي، حيث وجد أنه يحسن من تدفق سريان الدم داخل الشريان التاجي ولكنه أيضا يحسن من كفائة ووظيفة عضلة القلب ،كما يحسن ايضا من وظيفة صمامات القلب إذا كانت متأثرة بعد إحتشاء عضلة القلب.

الاستنتاج: يوصي باستخدام عقار الأدينوزين أثناء إجراء قسطرة تداخلية أولية في مرضى إحتشاء عضلة القلب الحاد المصاحب لإرتفاع مقطع إس تي لما له من فوائد عديدة على صحة المرضي.