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Intracoronary Pharmacotherapy (Verapamil-Epinephrine-Adenosine) for Prevention of No Reflow during Primary Percutaneous Coronary Intervention in Patients with ST Elevation Myocardial Infarction

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ABSTRACT

Background: When the TIMI flow is less than 3 or, in the instance of a flow of 3, when the MBG is 0 or 1, no reflow is detected (in the absence of evident vessel dissection, obstruction or distal vessel embolic cutoff). According to the TIMI flow count, the flow in the coronaries may be graded as 0 (no flow), 1 (penetration without perfusion), 2, or 3 (partial perfusion) (complete perfusion). Grade 0 indicates that there is no myocardial blush (or contrast density), while grade 1 indicates that there is continuing blush (staining) Grade 1 indicates the least amount of myocardial blush, grade 2 indicates significant myocardial blush (or contrast density), but less than that seen during angiography of a non-infarct-related coronary artery on the ipsilateral or contralateral side, and grade 3 indicates typical blush. **Patients and Methods:** This research included 128 individuals who had acute ST elevation myocardial infarction during the first 24 hours of experiencing symptoms and were treated at Wadi El-Nile and Ain Shams university hospitals between the years 2022 and 2023. In order to avoid STEMI patients from having no reflow during PPCI, the research compared the safety and effectiveness of intracoronary injections of epinephrine, verapamil, or adenosine against the control group. Aiming to evaluate TIMI flow grade, MBG, TIMI thrombus grade, ST segment resolution >70%, occurrence of no reflow, EF, LV diameters, and MACE status within 3 months, the study was conducted through 4 groups: group 1 received epinephrine, group 2 received adenosine, group 3 received verapamil, and group 4 did not receive pretreatment. **Results:** The epinephrine group, followed by the verapamil group, followed by the adenosine group, followed by the control group, had the best TIMI flow grade and MBG scores. After taking the medicines, there was no significant difference in the TIMI thrombus grade across the 4 groups. ST segment resolution varied quantitatively across the 4 groups, but there was no statistically significant difference. The three drugs—Epinephrine, Verapamil, and Adenosine—were all more successful than the control group when it came to preventing no reflow than they were individually. Between the 4 groups, there was no statistically significant difference in the EF and LV diameters. Within a 3-month period, there was no difference in the MACE status across the 4 groups. **Conclusion:** According to the available data, epinephrine, verapamil, and adenosine are safe and efficient in avoiding no-reflow in patients with ST Elevation Myocardial Infarction during PPCI, with epinephrine performing best, followed by verapamil, then adenosine. To verify these results, more research with a bigger sample size and a longer follow-up period is needed.

Keywords: Verapamil-Epinephrine-Adenosine Intracoronary Pharmacotherapy, No Reflow, Primary Percutaneous Coronary Intervention, ST Elevation Myocardial Infarction

Introduction

The gold standard for treating ST segment elevation myocardial infarction is primary percutaneous coronary intervention (PPCI) (STEMI). In more than 90% of patients, PPCI effectively restores cardiac tissue perfusion. A limited number of patients, nonetheless, continue to show overt myocardial reperfusion damage despite the effective opening of the infarct-related epicardial artery (IRA). No-reflow is a syndrome that is mostly brought on by severe micro vascular obstruction (MVO) **(Ramjane et al., 2008).** It usually results in considerable myocardial damage that impedes myocardial recovery and negatively affects Left ventricular remodelling. It is frequently present despite restoration of the coronary flow in the epicardial arteries. It could start occurring 1-2 hours after PCI is finished. If no reflow occurs in the catheterization lab, it is crucial to recognise it (Cath lab). A patient shouldn't ideally leave the Cath lab until any reflow has been adequately treated **(Galiuto et al., 2006).** No one method has been shown to be more effective than the others in controlling the no reflow problem. Numerous research are being conducted to decide which choice would be best in this situation.

The REMEDIA study was the first randomised experiment to evaluate the effectiveness of thrombectomy using a simple manual aspiration catheter. This research demonstrated that manual thrombectomy was safe and improved myocardial perfusion as compared to conventional primary PCI **(Werner et al., 2002).**

The pathophysiology of no reflow, which is known to include vasoconstriction of the distal capillary bed associated with distal embolization to the microcirculation, has historically been targeted by pharmacological methods. Numerous observational studies and randomised trials have looked at the possibility that the use of vasodilators, such as verapamil, papaverine, nicardipine, adenosine, and sodium nitroprusside, may improve microvascular function after an acute myocardial infarction **(Eeckhout and Kern, 2001).**

By enhancing coronary microcirculation and tissue perfusion, intracoronary epinephrine is regarded

as one of the safe and efficient choices in the treatment of no reflow with little to no major side effects and satisfactory angiographic results. In the development of embolization, platelet aggregation is crucial. The last process of platelet aggregation is blocked by glycoprotein Ib/a inhibitors (GPI), which also limit platelet activation, adhesion, and aggregation. This helps to reduce the likelihood of having an ischemic event and restore antegrade coronary flow of the blocked artery **(Hoffmann and Lefkowitz, 1996).**

Aim Of The Work

In order to avoid no reflow during PPCI in STEMI patients, this research compared the effectiveness and safety of intracoronary injections of epinephrine, verapamil, and adenosine.

Patients And Methods

In the years 2022 and 2023, 124 patients who had acute ST elevation myocardial infarction within the first 24 hours after experiencing symptoms were treated at Wadi El-Nile and Ain Shams University Hospitals. In order to avoid STEMI patients from having no reflow during PPCI, the research compared the safety and effectiveness of intracoronary injections of epinephrine, verapamil, or adenosine against the control group. Aiming to evaluate TIMI flow grade, MBG, TIMI thrombus grade, ST segment resolution >70%, occurrence of no reflow, EF, LV diameters, and MACE status within 3 months, the study was conducted through 4 groups: group 1 received epinephrine, group 2 received adenosine, group 3 received verapamil, and group 4 did not receive pretreatment.

Inclusion criteria

- Any patients who were at least 18 years old.
- Persistent chest pain is a symptom of myocardial ischemia, and an ECG showing ST-segment elevation in the following settings is indicative of STEMI: 2 contiguous leads with ST segment elevation 2.5 mm in men 40 years old, > 2 mm in men > 40 years old, or > 1.5 mm in women in leads V2-V3 and / or > 1 mm in all other leads **(Thygesen et al., 2012).**
- Angiographic imaging revealed that patients had a substantial intracoronary thrombus load with grade 3–5 thrombus. The angiographic thrombus load was divided into three categories: No thrombus, grade 0. Possible thrombus, Grade 1. Grade 2: the thrombus' largest dimension is less than half a vessel diameter; Grade 3: the largest dimension is between half and two vessel diameters; Grade 4: the largest dimension is more than two vessel diameters; Grade 5: the thrombus has completely blocked the vessel **(Sianos et al., 2010).**

Exclusion criteria

- execution of recuse PCI after thrombolysis.
- patients who had mechanical or dissection difficulties while having the operation.
- Epinephrine contraindications include HTN with SBP >180 mmHg and known epinephrine allergies.
- Verapamil contraindications include cardiogenic shock, hypotension with SBP 90 mmHg, severe bradycardia, and second- or third-degree heart block.
- Adenosine contraindications include adenosine allergy and second- or third-degree AV block.

Study tool and procedure:

All patients were required to fill out the following forms upon admission to the ER: a history form asking about name, age, gender, race, smoking status, diabetes, hypertension, renal impairment, a history of coronary artery disease, a drug history, a history of previous coronary interventions, and the date of the patient's first medical contact. physical examination, which includes a 12-lead ECG, local inspection, and vital signs laboratory testing, such as a random blood sugar test upon admission, a full blood count, and kidney function checks. Each patient got 300 mg of aspirin and either 90 or 600 mg of ticagrelor or clopidogrel. A skilled interventional cardiologist who conducts more than 75 PPCI annually admits patients for primary PCI **(Levine et al., 2011).**

Prior to PCI, each patient had routine left and right coronary angiograms with at least two best predictions. Patients were randomised into four groups by simple randomization as follows after the coronary artery was engaged, a guidewire was utilised to bridge the lesion, and a flow was established: Groups 1 and 2 each got 100 to 200 micrograms of epinephrine, 100 to 200 micrograms of verapamil, 100 to 200 micrograms of adenosine, and group 4 did not receive any pretreatment.

For greater tissue accessibility, verapamil, epinephrine, or adenosine were administered distal to the location of the lesion via a microcatheter. The study's main objective was to compare the incidence of no-reflow across groups (as measured by tissue perfusion using TIMI flow and/or MBG). The incidence of MACE during three months served as the secondary objective.

The flow in the coronaries is categorised by TIMI flow count into grades 0 (no flow), 1 (penetration without perfusion), 2, and 3 (full perfusion) **(Stone et al., 1998).** Grade 0 indicates that there is no myocardial blush (or contrast density), while grade 1 indicates that there is continuing blush (staining) Grade 1 refers to minimum myocardial blush, grade 2 to mild myocardial blush (or contrast density), and grade 3 to normal myocardial blush (or contrast density) **(Hof et al., 1998).**

When the TIMI flow is less than 3 or, in the event of a flow of 3, when the MBG is 0 or 1 (in the absence of an obvious vascular dissection, blockage, or distal vessel embolic cutoff), no reflow is detected **(Piana et al., 1994).** For monitoring, all patients were brought to the CCU, where they had echocardiograms to determine their baseline LVEF, which was determined using

Simpson's technique or 2D eyeballing. After three months, patients were invited to reschedule an appointment to evaluate their functional capacity, repeat an echo to determine their LVEF, and discuss MACE incidents. MACE was defined as the incidence of fatal MI, nonfatal stroke, and all-cause mortality.

Statistical Analysis

Data were gathered, edited, coded, and put into IBM SPSS version 23 of the Statistical Package for Social Science. When the quantitative data were parametric, they were shown as means, standard deviations, and ranges; when they were non-parametric, they were displayed as medians and interquartile ranges (IQR). Qualitative factors were also shown as percentages and numbers. As a result, the p-value was deemed significant: P>0.05 is regarded as non-significant (NS), P0.05 as significant (S), and P0.01 as very significant (HS).

RESULTS

A total of 128 patients were randomized into one of the following four groups: group 1 who received distal intracoronary administration of epinephrine; group 2 who received adenosine; group 3 who received verapamil; and group 4 who served as a control group.

Table (1) Demographic and clinical characteristics of the studied population.

Variable		**Total no=128**	**G-I no=32**	**G-II no=32**	**G-III no=32**	**G-IV no=32**	**P value**
Age (years)	Mean ± SD	56.82 ± 9.41	58.56 ± 8.78	56.88 ± 9.64	58.13 ± 10.13	53.72 ± 8.67	0.158
Gender	Male	103 (80.5%)	25 (78.1%)	26 (81.3%)	26 (81.3%)	26 (81.3%)	0.985
DM		54(42.2%)	15(46.9%)	15(46.9%)	12(37.5%)	12(37.5%)	0.764
HTN		60(46.9%)	13(40.6%)	16(50.0%)	17(53.1%)	14(43.8%)	0.740
Dyslipidemia		61(47.7%)	17(53.1%)	11(34.4%)	13(40.6%)	20(62.5%)	0.107
Smoking		99(77.3%)	22(68.8%)	22(68.8%)	25(78.1%)	30(93.8%)	0.054
FH of CAD		28(21.9%)	9(28.1%)	6(18.8%)	7(21.9%)	6(18.8%)	0.778
Total ischemic time (min)	Median(IQR)	450 (240 - 720)	480(180 - 720)	720(360 - 720)	420(240 - 720)	270(150 - 660)	0.091
	Range	60-2160	12-1440	120-1080	120-2160	60-1440	
Door-to-balloon time (min)	Mean ± SD	34.45 ± 7.51	34.69 ± 8.03	34.69 ± 8.03	33.75 ± 6.09	34.69 ± 8.03	0.947
STEMI location	Anterior	83(64.8%)	19(59.4%)	22(68.8%)	21(65.6%)	21(65.6%)	**0.040**
	Lateral	9(7.0%)	2(6.3%)	6(18.8%)	0(0.0%)	1(3.1%)	
	Inferior	36(28.1%)	11(34.4%)	4(12.5%)	11(34.4%)	10(31.3%)	
Killip class	Killip class 1	127(99.2%)	31(96.9%)	32(100%)	32(100%)	32(100%)	0.388
	Killip class 2	1(0.8%)	1(3.1%)	0(0.0%)	0(0.0%)	0(0.0%)	
	Killip class 3	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	
	Killip class 4	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	
Type of P2Y12 inhibitor	Ticagrelor	103(80.5%)	26(81.3%)	25(78.1%)	27(84.4%)	25(78.1%)	0.908
	Clopidogrel	25(19.5%)	6(18.8%)	7(21.9%)	5(15.6%)	7(21.9%)	
SBP (mmHg)	Mean ± SD	127.70 ± 13.87	122.81 ± 13.50	129.22 ± 13.02	129.22 ± 13.02	129.53 ± 15.31	0.151
DBP (mmHg)	Mean ± SD	78.44 ± 10.97	74.38 ± 12.68	80.00 ± 10.16	80.00 ± 10.16	79.38 ± 10.14	0.114
HR (bpm)	Mean ± SD	85.09 ± 8.48	85.16 ± 10.45	85.06 ± 7.64	85.06 ± 7.64	85.06 ± 8.30	1.000
LVESD (mm)	Mean ± SD	38.09 ± 5.49	38.19 ± 6.00	39.19 ± 4.29	37.84 ± 5.18	37.16 ± 6.32	0.521
LVEDD (mm)	Mean ± SD	46.59 ± 3.42	46.44 ± 4.16	47.66 ± 2.54	46.00 ± 3.18	46.28 ± 3.54	0.225
LVEF (%)	Mean ± SD	37.30 ± 8.82	36.88 ± 8.01	39.38 ± 10.26	36.88 ± 7.91	36.09 ± 8.96	0.476

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)

	Post Hoc analysis by LSD					
	Group 1 Vs Group 2	**Group 1 Vs Group 3**	**Group 1 Vs Group 4**	**Group 2 Vs Group 3**	**Group 2 Vs Group 4**	**Group 3 Vs Group 4**
STEMI location	0.064	0.350	0.786	**0.010**	**0.046**	0.592

The mean age was 58.56 8.78, 56.88 9.64, 58.13 10.13, and 53.72 8.67 in groups 1, 2, 3, and 4, respectively, and 78.1 %, 81.3 %, 81.3 %, and 81.3 %, respectively, of them were males. With p-values of 0.158 and 0.985, respectively, no statistically significant difference was found between the four studied groups regarding age and gender distribution. In groups 1, 2, 3, and 4, the percentage of DM was 46.9%, 46.9%, 37.5%, and 37.5%, respectively. The percentage of HTN was 40.6 percent, 50.0 percent, 53.1 percent, and 43.8 percent, and the percentage of dyslipidemia was 53.1%, 34.4 percent, 40.6 percent, and 62.5 percent. The percentage of smokers was 68.8%, 68.8%, 78.1 percent, and 93.8 percent, respectively.

The median door to balloon time was 34.69 8.03 minutes, 34.69 8.03 minutes, 33.75 6.09 minutes, and 34.69 8.03 minutes in groups 1, 2, 3, and 4, respectively. There was no statistically significant difference between the four examined groups, with p-values = 0.091 and 0.947, respectively. The most common STEMI location was anterior, with 59.4 percent, 68.8 percent, 65.6 percent, and 65.6 percent in groups 1, 2, 3, and 4, respectively. Lateral STEMI was next, with 6.3 percent, 18.8 percent, 0.0 percent, and 3.1 percent, respectively, which was shown to be statistically significant.

In groups 1, 2, 3, and 4, respectively, 81.3 percent, 78.1 percent, 84.4 percent, and 78.1 percent of the patients were taking ticagrelor, and 18.8 percent, 21.9 percent, 15.6 percent, and 21.9 percent, respectively, were taking clopidogrel. However, there was no statistically significant difference between the four groups under study, with a p-value of 0.90. 96.9%, 100%, 100%, and 100% of the patients in groups 1, 2, 3, and 4 correspondingly all had Killip class 1, and there was no statistically significant difference between the four groups under study (p-value = 0.388).

In groups 1, 2, 3, and 4, the mean SBP was 122.81 13.50, 129.22 13.02, 80.00 10.16, and 80.00 10.16 mmhg, respectively. The mean DBP was 74.38 12.68, 80.00 10.16, 80.00 7.64, and 80.00 8.30 bpm, respectively. There was no statistically significant difference between the four studied groups regarding the hemodynamics, with p There was no statistically significant difference in the echo results between the four studied groups, with p-values of 0.521, 0.225, and 0.476, respectively. The mean LVESD was 38.19 6.00, 39.19 4.29, 37.84 5.18, and 37.16 6.32 mm in groups 1, 2, 3, and 4, respectively. The mean LVEDD was 46.44 4.16, 47.66 2.54, 46.00 3.

Table (2) Baseline procedural characteristics of the studied population.

Variable		Total no=128	G-I no=32	G-II no=32	G-III no=32	G-IV no=32	P value
Number of vessels affected	1 vessel	79(61.7%)	23(71.9%)	19(59.4%)	14(43.8%)	23(71.9%)	0.065
	2 vessels	49(38.3%)	9(28.1%)	13(40.6%)	18(56.3%)	9(28.1%)	
Culprit vessel	LAD	82(64.1%)	20(62.5%)	22(68.8%)	19(59.4%)	21(65.6%)	0.900
	LCX	11(8.6%)	3(9.4%)	3(9.4%)	3(9.4%)	2(6.3%)	
	RCA	31(24.2%)	8(25.0%)	5(15.6%)	10(31.3%)	8(25.0%)	
	OM	4(3.1%)	1(3.1%)	2(6.3%)	0(0.0%)	1(3.1%)	
	Diagonal	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	
Balloon use		74(57.8%)	21(65.6%)	20(62.5%)	16(50.0%)	17(53.1%)	0.536
Stent use		128(100.0%)	32(100.0%)	32(100.0%)	32(100.0%)	32(100.0%)	NA
Type of stent	DES	128(100.0%)	32(100.0%)	32(100.0%)	32(100.0%)	32(100.0%)	NA
TIMI thrombus grade before drug	TIMI thrombus 3	18(14.1%)	5(15.6%)	6(18.8%)	5(15.6%)	2(6.3%)	0.624
	TIMI thrombus 4	31(24.2%)	10(31.3%)	5(15.6%)	8(25.0%)	8(25.0%)	
	TIMI thrombus 5	79(61.7%)	17(53.1%)	21(65.6%)	19(59.4%)	22(68.8%)	
Thrombus aspiration		0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	NA
TIMI flow grade before drug	TIMI flow 0	74(57.8%)	17(53.1%)	16(50.0%)	19(59.4%)	22(68.8%)	0.457
	TIMI flow 1	14(10.9%)	6(18.8%)	3(9.4%)	2(6.3%)	3(9.4%)	
	TIMI flow 2	40(31.3%)	9(28.1%)	13(40.6%)	11(34.4%)	7(21.9%)	
Average stent(s) diameter (mm)	Mean ±SD	2.93 ± 0.29	2.89 ± 0.28	2.96 ± 0.28	2.96 ± 0.28	2.92 ± 0.31	0.725
Average stent(s) length (mm)	Mean ±SD	32.03 ± 8.15	32.94 ± 8.15	31.91 ± 7.96	31.88 ± 8.58	31.41 ± 8.20	0.898
TIMI thrombus grade after drug	TIMI thrombus 3	30(23.4%)	9(28.1%)	8(25.0%)	11(34.4%)	2(6.3%)	0.133
	TIMI thrombus 4	43(33.6%)	10(31.3%)	9(28.1%)	8(25.0%)	16(50.0%)	
	TIMI thrombus 5	55(43.0%)	13(40.6%)	15(46.9%)	13(40.6%)	14(43.8%)	

	TIMI flow 1	14(10.9%)	2(6.3%)	5(15.6%)	4(12.5%)	3(9.4%)	0.658
TIMI flow grade after drug	TIMI flow 2	41(32.0%)	5(15.6%)	11(34.4%)	4(12.5%)	21(65.6%)	**<0.01**
	TIMI flow 3	73(57.0%)	25(78.1%)	16(50.0%)	24(75.0%)	8(25.0%)	**<0.01**
	MBG 0	17(13.3%)	3(9.4%)	2(6.3%)	3(9.4%)	9(28.1%)	**0.039**
MBG	MBG 1	22(17.2%)	3 (9.4%)	2(6.3%)	3(9.4%)	14(43.8%)	**<0.01**
	MBG 2	32(25.0%)	4 (12.5%)	13(40.6%)	12(37.5%)	3(9.4%)	**0.003**
	MBG 3	57(44.5%)	22(68.8%)	15(46.9%)	14(43.8%)	6(18.8%)	**<0.01**
No-reflow occurrence		55(43.0%)	7(21.9%)	16(50.0%)	8(25.0%)	24(75.0%)	**<0.01**

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)

	Post Hoc analysis by LSD					
	Group 1 VsGroup 2	**Group 1 VsGroup 3**	**Group 1 VsGroup 4**	**Group 2 VsGroup 3**	**Group 2 VsGroup 4**	**Group 3 Vs Group 4**
TIMI flow 2	0.083	0.719	**<0.01**	**0.039**	**0.012**	**<0.01**
TIMI flow 3	**0.019**	0.768	**<0.01**	**0.039**	**0.039**	**<0.01**
MBG 0	0.641	1.000	0.055	0.641	**0.020**	0.055
MBG 1	0.641	1.000	**0.002**	0.641	**0.001**	**0.002**
MBG 2	**0.011**	**0.021**	0.689	0.797	**0.004**	**0.008**
MBG 3	0.076	**0.043**	**<0.01**	0.802	**0.017**	**0.031**
	Post Hoc analysis by LSD					
	Group 1 VsGroup 2	**Group 1 VsGroup 3**	**Group 1 VsGroup 4**	**Group 2 VsGroup 3**	**Group 2 VsGroup 4**	**Group 3 Vs Group 4**
No-reflow occurrence	**0.019**	0.768	**<0.01**	**0.039**	**0.039**	**<0.01**

The majority of the patients had single vessel disease; in groups 1, 2, 3, and 4, the percentages were 71.9 percent, 59.4 percent, 43.8 percent, and 71.9 percent, respectively; the percentages of patients who had two vessel disease were 28.1 percent, 40.6 percent, 56.3 percent, and 28.1 percent, respectively; there was no statistically significant difference between the four groups with a p-value of 0.065. The LAD was the most frequently observed culprit vessel, accounting for 62.5 percent, 68.8 percent, 59.4 percent, and 65.6 percent in Groups 1, 2, 3, and 4, respectively. The RCA, LCX, and OM were the next most prevalent culprit vessels, with no statistically significant differences between the four groups under study (p-value = 0.900).

Before receiving the medication, the majority of patients had TIMI thrombus grade 5; in groups 1, 2, and 3, this percentage was 53.1%, followed by 65.6%, 59.4%, and 68.8%; in groups 1, 3, and 4, it was 53.1%, 50.0%, 59.4%, and 68.8%; there was no statistically significant difference between the four groups with p-values of 0.624 and 0.457, respectively. Although not all patients required thrombus aspiration, the majority of patients underwent balloon dilatation: 65.6 percent, 62.5 percent, 50.0 percent, and 53.1 percent in groups 1, 2, 3, and 4, respectively. There was no statistically significant difference between the four studied groups, with a p-value of 0.536.

All patients underwent coronary DES, with mean stent diameters of 2.89 mm, 2.96 mm, 2.96 mm, and 2.92 mm in groups 1, 2, and 3, and lengths of 32.94 mm, 31.91 mm, 7.96 mm, 8.58 mm, and 31.41 mm, respectively. There was no statistically significant difference between the four groups under study, with p-values of 0.725 and 0.898, respectively. TIMI 3 flow was 78.1 percent, 50.0 percent, 75.0 percent, and 25.0 percent in groups 1, 2, and 3 respectively. This was significantly higher with group 1 than group 2 and 4 with p-values of 0.019 and 0.01, respectively, and significantly higher with group 3 than group 2 and 4 with p-values of 0.039 and 0.01, respectively. However, this difference was not statistically significant.

MBG 3 was 68.8 %, 46.9 %, 43.8 %, and 18.8 % in Groups 1, 2, 3, and 4, respectively. This was statistically higher with Group 1 than Groups 3 and 4 with p-values of 0.043 and 0.01, respectively, significantly higher with Group 2 than Group 4 with p-values of 0.017 and 0.031, and significantly higher with Group 3 than Group 4 with p-values of 0.031, but not MBG 2 was 12.5%, 40.6%, 37.5%, and 9.4% in Groups 1, 2, 3, and 4, respectively. It was statistically higher in Group 2 than in Groups 1 and 4 with p-values of 0.011 and 0.004, respectively, and significantly higher in Group 3 than in Groups 1 and 4 with p-values of 0.021 and 0.008, respectively. However, there was no statistically significant difference between Group 2 and Group 3 with a p-value of 0.7

No-reflow has occurred in 21.9 percent, 50.0 percent, 25.0 percent, and 75.0 percent in groups 1, 2, 3, and 4, respectively. This was significantly lower with group 1 than groups 2 and 4 with p-values of 0.019 and 0.01, respectively, and significantly lower with group 3 than groups 2 and 4 with a p-value of 0.039 and 0.039, respectively.

Table (3) In-hospital and 3 months' outcomes of the studied population.

Variable		Total no=128	G-I no=32	G-II no=32	G-III no=32	G-IV no=32	P value
ST resolution >70%		88(68.8%)	25(78.1%)	22(68.8%)	24(75.0%)	17(53.1%)	0.137
Status of MACE		30(23.4%)	7(21.9%)	5(15.6%)	8(25.0%)	10(31.3%)	0.519
Type of MACE	CV death	10(33.3%)	4(57.1%)	2(40.0%)	3(37.5%)	1(10.0%)	0.486
	Repeat revasc.	2(6.7%)	0((0.0%)	0(0.0%)	0(0.0%)	2(20.0%)	
	Recurrent MI	4(13.3%)	0(0.0%)	1(20.0%)	1(12.5%)	2(20.0%)	
	HF hospital	14(46.7%)	3(42.9%)	2(40.0%)	4(50.0%)	5(50.0%)	

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)

There was no statistically significant difference between the four studied groups for the in-hospital and three-month outcomes, with p-values of 0.137 and 0.519, respectively. ST-segment resolution > 70% was seen in 78.1 percent, 68.8 percent, 75.0 percent, and 53.1 percent of patients in groups 1, 2, 3, and 4. MACE occurred in 21.9 percent, 15.6 percent, 25.0 percent, and 31.3 percent of patients.

Regarding the kind of MACE, either CV mortality, repeated revascularization, recurrent MI, or HF hospitalisation, there was no statistically significant difference between the four groups (p value = 0.486).

Table (4) Time to occurrence of mace (months) using Kaplan-Meier analysis

Total N	N. of Events	Mean	SE	95% CI Lower	Upper	Survival at 1 month	2months	3 months
128	30	20.990	1.031	18.970	23.010	85.1%	80.4%	77.2%

	Total no.	N. of events	Mean	SE	95% CI Lower	95% CI Upper	Log Rank test Test value	Log Rank test P-value	Log Rank test Sig.
Group1 (Epinephrine)	32	7	21.339	2.023	17.374	25.304			
Group2 (Adenosine)	32	5	2.783	0.154	2.482	3.085	2.120	0.548	NS
Group3 (Verapamil)	32	8	2.403	0.211	1.989	2.817			
Group4 (control)	32	10	2.622	0.195	2.240	3.004			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)

There was no statistically significant difference found between the four studied groups regarding the time to occurrence of MACE with p-value = 0.548.

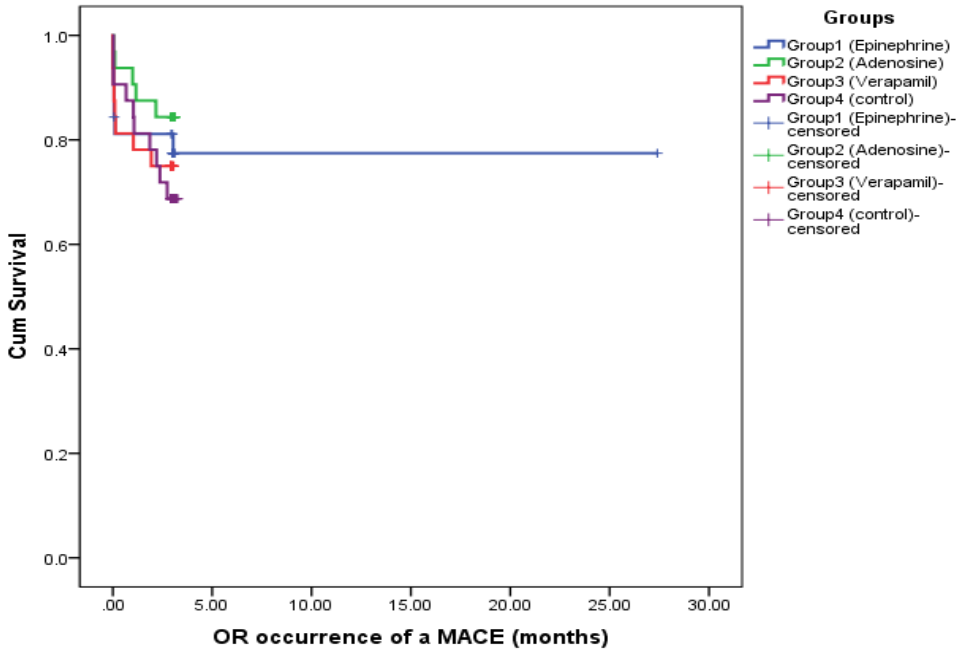


Figure (1): Comparison between the four studied groups regarding time to occurrence of mace (months) using Kaplan-Meier analysis

CASE 2

History:

- 59-year-old male
- DM
- Dyslipidemic
- Presented with Anterior STEMI KILLIP I on 23/4/2022

Complaint:

Patient presented with typical chest pain of 8 hours duration.

Clinical examination:

BP: 120/80, HR: 90 BPM regular, Chest was clear, Normal heart sounds, with no lower limb edema.

ECG:

ST segment elevation in leads v1-v6, ST segment depression in leads II, III and avf.

Echo:

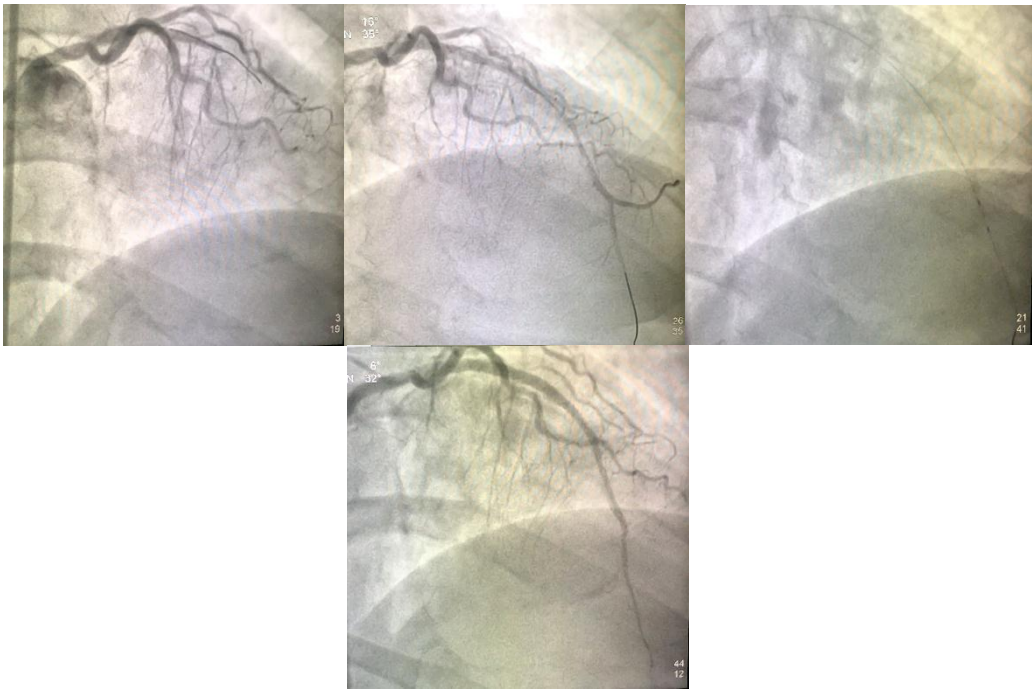
EF: 30% by 2D, LVEDD: 46 mm and LVESD: 39 mm.

Coronary angiography:

LAD: Atherosclerotic vessel with mid total occlusion, LCX: Atherosclerotic vessel with non-significant lesions, RCA: Atherosclerotic vessel with non-significant lesions.

PCI:

PTCA was done to mid LAD by 2 x 15 mm balloon, over the wire balloon was used to inject Epinephrine distal to the site of the occlusion, stenting was done to mid LAD by 1 DES 2.75 x 28 mm, with TIMI 3 flow and MBG 3.



Follow up within 3 months:

Patient came for clinical follow up on 23/7/2022 with fair functional capacity, no improvement in the EF and no MACE had occurred.

DISCUSSION

When the TIMI flow is less than 3 or, in the instance of a flow of 3, when the MBG is 0 or 1, no reflow is detected (in the absence of evident vessel dissection, obstruction or distal vessel embolic cutoff).

The flow in the coronaries is categorised by TIMI flow count into grades 0 (no flow), 1 (penetration without perfusion), 2, and 3 (full perfusion) **(Stone et al., 1998).**

Myocardial blush grade divides coronary flow into grade 0, which denotes a lack of myocardial blush (or contrast density), grade 1, which denotes a minimal blush, grade 2, which denotes a moderate blush (or contrast density), but one that is less than that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery, and grade 3, which denotes a normal blush **(Hof et al., 1998).**

No-reflow patients are the highest-risk subset of patients needing reperfusion and must be prevented and treated in order to reduce their risk of early death and morbidity **(Tascanov et al., 2019).** The no-reflow phenomena has been linked to cardiac failure and ventricular arrhythmias **(Sabin et al., 2017).** Even worse, evidence suggests that it could have a detrimental effect on left ventricular remodelling after AMI **(Morishima et al., 2000).** In follow-up studies, the no-reflow phenomena has been connected to dangerous arrhythmias, a lower ejection fraction, and a greater risk of cardiac mortality. Treatment for no-reflow increases myocardial perfusion, which promotes functional muscle regeneration and slows infarct enlargement, accelerating the healing process (Heward and Widrich, 2020). Sufficient myocardial perfusion also improves survival in individuals with acute MI **(Abu Arab, 2016).**

This research included 128 individuals who had acute ST elevation myocardial infarction during the first 24 hours of experiencing symptoms and were treated at Wadi El-Nile and Ain Shams university hospitals between the years 2022 and 2023. The research, which

compared the effectiveness and safety of intracoronary injections of epinephrine, verapamil, or adenosine against the control group for the prevention of no reflow after PPCI in STEMI patients, was a randomised prospective trial. Aiming to evaluate TIMI flow grade, MBG, TIMI thrombus grade, ST segment resolution >70%, occurrence of no reflow, EF, LV diameters, and MACE status within 3 months, the study was conducted through 4 groups: group 1 received epinephrine, group 2 received adenosine, group 3 received verapamil, and group 4 did not receive pretreatment.

By the time our research was being conducted, no previous studies had the same methodology for administering epinephrine, verapamil, or adenosine, as well as a follow-up strategy. In our study, we used Epinephrine, Verapamil, or Adenosine as medications to improve no reflow in STEMI patients (prophylactic, not therapeutic), and our results demonstrated that when the studied groups were compared in terms of TIMI thrombus grade, TIMI flow grade, MBG, and no-reflow occurrence, there was a significant improvement regarding the flow and perfusion with the 3 groups (versus the control group), with better outcomes in the Epine

MGB III was numerically higher with Epinephrine than Adenosine but not statistically significantly (68.8 percent vs. 46.9 percent); (p = 0.076), numerically higher with Adenosine than Verapamil but there was no statistically significant difference (46.9 percent vs. 43.8 percent); (p = 0.802), and highly significant higher with Epinephrine than the control group (68.8 percent vs. 18.8

MBG II was numerically higher with Adenosine than Verapamil with no statistically significant difference (40.6 percent vs. 37.5 percent); (p = 0.011), significantly higher with Adenosine than Epinephrine (40.6 percent vs. 12.5 percent); and (p = 0.797), there was no statistically significant difference between Epinephrine and the control group (12.5 percent vs. 9.4 percent).

Between the 4 groups, the TIMI thrombus grade was not significant (p = 0.333).

(p = 0.768), significantly lower with Epinephrine than Adenosine (21.9 percent vs 50 percent); (p = 0.019), significantly lower with Verapamil than Adenosine (25 percent vs 50 percent); (p = 0.039), highly significant lower with Epinephrine than the control group (21.9 percent vs 75 percent); (p = 0.0.1), highly significant lower with Epinephrine than the Verapamil group (2

In a comparison of the examined groups, Epinephrine had a numerically greater ST resolution >70% rate (78.1%) than Verapamil (75%), Adenosine (68.8%), Adenosine (68.8%), and the control group (53.1%), although there was no statistically significant difference between the 4 groups (p = 0.137). ECHO findings, EF, and LV diameter comparisons across the four study groups were not statistically significant (p = 0.476). MACE is defined as the occurrence of all-cause death, non-fatal MI, and non-fatal stroke within a 3-month period. When comparing the studied groups, Adenosine had the lowest MACE rate (15.6%), followed by Epinephrine (21.9%), Verapamil (25%) and the control group (31.3%), but there was no statistically significant difference between the 4 groups (p = 0.519).

The effectiveness of epinephrine against verapamil in preventing no reflow was examined in the study by Yassin et al. (2021) as follows: Distal Intracoronary Delivery of Epinephrine versus Verapamil to Prevent No-Reflow During Primary Percutaneous Coronary Intervention.

A total of 120 participants participated in this trial. The patients were randomly assigned to one of three groups: group I got epinephrine administered distally intracoronarily; group II received verapamil; and group III acted as the control group. This trial had 120 patients and its main outcome was the incidence of no-reflow, which was defined as a post-procedural TIMI flow grade (TFG) of 3 or, in the event of a TFG of 3, a TIMI myocardial perfusion grade (TMPG) of 0 or 1. Groups I and II significantly outperformed the control group in terms of angiographic flow and perfusion parameters, with the epinephrine group showing the best results. TMPG3 was significantly higher with epinephrine than verapamil (55 percent) (p = 0.037), and TMPG2 was higher in verapamil than epinephrine (7.5 percent) (p = 0.003). With verapamil, no reflow is lower (25% vs. 27.5%), but there is no statistically significant difference between the two (P=0.785). There is no statistically significant difference between the patients in the three groups regarding hospitalisation for heart failure or (MACE) (ST-segment resolution with 90 minutes following reperfusion, LVEDD, LVESD and EF). With the exception of adenosine, these results agreed with our findings.

The effectiveness of adenosine in preventing no reflow was examined in the research by Hatata et al. (2023) as follows: Role of Intra-Coronary Adenosine on prevention of No Reflow during Primary PCI in STEMI Patients Guided by MVO in CMR.

In this research, 50 patients participated. The patients were divided into two groups by randomization: group A received adenosine routinely following the establishment of TIMI I flow, either naturally or by passing a wire or non-inflated balloon through a catheter to the distal coronary bed; group B had not received adenosine, and MRI was performed within 48 hours of primary PCI and again for follow-up three months later. Although the TIMI and MBG scores did not significantly change between the two groups, the myocardial salvage index and myocardium at risk did, with a p value less than 0.001. But neither group's myocardial bleeding increased. In those who received adenosine, the EF, LV mass, and LV volumes were significantly improved. Instead of relying just on angiographic success, he employed CMR to examine the no reflow phenomenon. While there were improvements in MVO and MV haemorrhage within

CMR as well as EF and LV remodelling, there were no statistically significant alterations in TIMI and MBG grades. He solely utilised adenosine in this investigation, which agreed with ours in terms of the efficacy of the intracoronary drug and the lack of reflow prevention. They employed fewer patients, which made it different from our research in terms of how adenosine improved the TIMI flow grade and MGB. The follow-up time in his research allowed for the measurement of LV remodelling and improvement of EF and LV diameters by CMR, which is more accurate than 2D and Simpson's technique echocardiography. This made it distinct from our study in this regard. He did not evaluate MACE the same way we did for our research.

Comparison of Intracoronary Epinephrine and Adenosine for No-Reflow in Normotensive Patients with Acute Coronary Syndrome by **Khan et al. (2022)** looked into the effectiveness of one medication over the other for treating no reflow (COAR Trial).

The 201 patients in this research had no reflow. Following a one-month observation period, the patients were randomly assigned 1:1 to receive intracoronary epinephrine as the therapy and intracoronary adenosine as the control. Improvements in coronary flow were measured primarily by frame counts, myocardial blush, and TIMI (Thrombolysis in Myocardial Infarction) flow. Major adverse cardiac events, in-hospital mortality, and short-term mortality were secondary endpoints. In all, 100 patients got adenosine, while 101 individuals received intracoronary epinephrine. Epinephrine was typically well tolerated, with no ventricular fibrillation or immediate table death. With final TIMI III flow (90.1 percent against 78 percent, P=0.019) and final corrected TIMI frame count (24.8.43 versus 26.639.22, P=0.036), no-reflow was more successfully improved with epinephrine. The final grade III myocardial blush (55.4 against 45 percent, P=0.139), the mean decrease of corrected TIMI frame count (25.71 compared 26.08 versus P=0.825), the in-hospital and short-term mortality, and the main adverse cardiac events, however, did not show any significant differences. The epinephrine group's EF improved more, as determined by echocardiography at the follow-up. In this investigation, the administration of epinephrine in patients with normotensive no-reflow was shown to be comparatively safe. It exhibits substantially superior effectiveness than adenosine due to a considerably larger frequency of post-treatment TIMI III flow grade, a lower final corrected TIMI frame count, and a relatively better accomplishment of myocardial blush grade III. This research was in agreement with ours, with the exception that our study did not test EF after 30 days, but their study did. In their trial, intracoronary drugs were employed to treat no reflow rather than to prevent it.

In **Darwish et al. (2022),** they conducted the following single-center retrospective cohort research to compare the effectiveness of intracoronary epinephrine and adenosine in the therapy of refractory no reflow phenomena.

On 156 patients who had refractory no-reflow following initial PCI, this research was done. The research comprised STEMI patients who received either intracoronary epinephrine or adenosine and experienced refractory no-reflow phenomena after initial PCI after failing standard therapies. 65 of 75 patients (86.7%) who received adenosine and 74 of 81 (91.4%) patients who received epinephrine successfully underwent reperfusion (P .05). After receiving epinephrine, 56 of 81 patients (69.1%) were able to attain TIMI III flow, as opposed to 39 of 75 patients (52.7%) in the adenosine group (P=.04). In the epinephrine group, the incidence of heart failure was lower than in the adenosine group (6.3 percent vs. 19.2 percent, P=.017) after a year of follow-up. Patients who got epinephrine compared to those who received adenosine had decreased rates of MACE after a year of follow-up (11.3 percent Vs. 26.7 percent, P.01).

Intracoronary epinephrine, which has a better long-term prognosis than adenosine, was just as beneficial as adenosine after initial PCI in managing the refractory no-reflow syndrome. The MACE in this study's epinephrine group was superior than that in the control group after a year of follow-up, but there was no statistically significant difference in the EF between the groups at that time (P=.0179). In addition, TIMI and MBG were better in the epinephrine group, which was consistent with our research's angiographic results. However, MACE was not significant in our study since it was evaluated after a shorter (3 month) period of follow-up.

Su et al(2013) .'s study, titled Short-term Effect of Verapamil on Coronary no reflow Associated with Percutaneous Coronary Intervention in Patients with Acute Coronary Syndrome: A Systematic Review and Meta-analysis of Randomized Controlled Trials, examined the effectiveness and safety of intracoronary verapamil injection in the prevention and treatment of coronary no-reflow after percutaneous coronary intervention (PCI).

539 individuals from 7 studies were included in the study. In addition to lowering the corrected thrombolysis in myocardial infarction (TIMI) frame count (CTFC) (weighted mean difference: 11.62; 95 percent confidence interval [CI]]: 16.04 to 7.21) and improving the TIMI myocardial perfusion grade (TMPG), verapamil treatment was significantly more effective in reducing the incidence of no-reflow (RR: 0.43; 95 percent CI: 0.29 to 0.64). In comparison to the control, verapamil also decreased the 30-day wall motion index (WMI). Additionally, the operation decreased the frequency of serious adverse cardiac events (MACEs) in ACS patients while they were hospitalised (RR: 0.37; 95 percent CI: 0.17 to 0.80) and two months following PCI (RR: 0.56; 95 percent CI: 0.33 to 0.95). Regardless of how long it had been after PCI, administering verapamil did not result in a further improvement in left ventricular ejection fraction. Verapamil injection given intracoronarily helps avoid no-reflow/slow-flow, reduce WMI, lower CTFC, and

improve TMPG. Additionally, it is probably going to lower the 2-month MACEs in ACS patients after PCI. This study was similar to ours in that it improved TIMI and MBG scores, but it did not solely rely on angiographic findings. It also assessed wall motion index and corrected thrombolysis in myocardial infarction (TIMI) frame count, both of which showed significant improvement. It also claimed that MACE improved within two months, which was different from our study because a larger number of patients were enrolled in it.

CONCLUSION

According to the available data, epinephrine, verapamil, and adenosine are safe and efficient in avoiding no-reflow in patients with ST Elevation Myocardial Infarction during PPCI, with epinephrine performing best, followed by verapamil, then adenosine. To verify these results, more research with a bigger sample size and a longer follow-up period is needed.

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