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Distal Intracoronary Delivery of Epinephrine versus Verapamil to Prevent No-Reflow During Primary Percutaneous Coronary Intervention: A Randomized, Open-Label, Trial

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ABSTRACT

Background: *Previous trials showed a promising potential use of epinephrine in the treatment of no-reflow phenomenon (the no-reflow phenomenon is multiple pathogenetic processes, which may be attributed to ischemic injuries, distal atherothrombotic embolization, coronary-microcirculation susceptibility to injury, and reperfusion injuries (6)). This study aimed to compare the safety and efficacy of distal intracoronary delivery of epinephrine versus verapamil to prevent no-reflow during primary percutaneous coronary intervention (PPCI).*

Materials and Methods*: We conducted a randomized, open-label, trial on patients undergoing PPCI. Patients were randomized to one of three groups: group I who received distal intracoronary administration of epinephrine; group II who received verapamil; and group III who served as a control group. The primary endpoint in our study was the incidence of no-reflow, defined as a post-procedural (Thrombolysis in Myocardial Infarction) TIMI flow grade (TFG) is < 3 or, in the case of a TFG of 3, when TIMI myocardial perfusion grade (TMPG) is 0 or 1.*

Results*: A total of 120 patients were randomized. The angiographic flow and perfusion parameters were significantly improved in group I and II versus the control group, with better results in epinephrine group only TMPG3 was significantly higher with epinephrine (77.5%) than verapamil (55%) (p = 0.037) and TMPG2 was higher in verapamil (32.5%) than epinephrine (7.5%) (p = 0.003). No reflow is lower with epinephrine than verapamil (25% vs 27.5%); however, with no statistically significant difference (P=0.785). Patients in the three groups has no statistical significant difference in (MACE) or heart failure hospitalization.*

Conclusion*: Epinephrine and verapamil are safe and effective in managing patients with no-reflow during PPCIs. Further studies with a larger sample and a longer duration of follow-up are required to confirm these findings.*

Introduction

The absence of myocardial perfusion despite opening the epicardial coronary arteries during the percutaneous coronary intervention (PCI) is known as the no-reflow phenomenon [1,2]. The rate of no-reflow after elective PCIs is estimated to be between 0.6 and 5%; however, in primary PCI (PPCI) cases, it may be observed in up to 50% [3]. Myocardial no-reflow correlates with worse contractile failure and increased complication risk and is an independent marker of PCI-induced mortality and myocardial infarction [4]. The main adverse event of the no-reflow phenomenon is the elimination of the positive effects of PCI [5]. The no-reflow phenomenon is multiple pathogenetic processes, which may be attributed to ischemic injuries, distal atherothrombotic embolization, coronary-microcirculation susceptibility to injury, and reperfusion injuries [6]. Recently, many studies focused on thrombus aspiration to prevent the distal embolization of thrombotic/plaque material [7,8]. In addition, multiple studies have evaluated the beneficial impact of systemic or intracoronary drug micro-circulation, affecting various cell types as platelets or serving as vasodilators [9,10].

In 1989, Wilson and his colleagues reported the first application of vasodilator (papaverine) in a case of no-reflow, using papaverine, showing a favorable response [11]. Furthermore, several vasodilators, including adenosine, nitrate, nicardipine, and verapamil, have been investigated to test their effect on no-reflow cases since then (12). Verapamil is a calcium channel blocker that induces significant vasodilation in the coronary arteries and treats no-reflow [13]. However, it is interesting that some vasoconstrictors may also play a role in coronary vasodilation by acting on certain receptors. Epinephrine is a beta-2 receptor agonist with potent effects, which mediate arteriolar vasodilation [14]. Moreover, epinephrine acts on beta-1 receptors, leading to inotropic and chronotropic stimulation of the myocardium [15]. Despite the fact that epinephrine has been used to treat cardiopulmonary arrest, a few studies have reported its efficacy in coronary no-reflow [2,3]. The findings of these studies indicated a promising potential use of epinephrine in the treatment of no-reflow. These trials, however, had many limitations and yielded inconclusive findings. Therefore, this study aimed to compare the safety and efficacy of distal intracoronary delivery of epinephrine vs. verapamil to prevent no-reflow during PPCIs.

Materials and Methods:

The protocol of the study was approved by the Ethical Committee of General organization of teaching hospitals, Cairo, Egypt (**REC IHC00003**). The study's objectives and procedures were explained in detail for all eligible patients; only patients who agreed to sign the written informed consent were included. We confirm that none of the study's procedures violated the main principles of the Declaration of Helsinki [16].

Study design and patients

We conducted a randomized, open-label trial on patients presenting with ST-elevated acute myocardial infarction (STEMI), who were scheduled to undergo PPCI at the National Heart institute, Giza, Egypt. The recruitment period lasted for one year from January to December 2019. Adult patients were deemed eligible if they met the following criteria: patients with acute STEMI within 12 hours of onset of chest pain undergoing PPCI; and patients with significant lesion that indicate local thrombosis. We excluded patients with tachyarrhythmias, cardiogenic shock, and/or increased blood pressure (> 160/90mmHg).

Eligible patients were randomized to one of three groups each containing 40 patients: group I who received distal intracoronary administration of epinephrine; group II who received verapamil; and group III who served as a control group.

Preoperative assessment and study's interventions

Complete medical reports of all eligible patients were fulfilled. Patients were asked for history taking, full clinical examination, routine laboratory investigations, baseline 12-lead electrocardiogram ECG findings., echocardiography, and diagnostic coronary angiography Besides, the baseline hemodynamics (heart rate and systolic blood pressure) and angiographic indices of coronary flow and myocardial perfusion (TIMI flow grade (TFG), corrected frame count (cTFC), myocardial perfusion grade (TMPG), thrombus grade (TTG)) were recorded. Patients were instructed to take the following pre-procedure medications: aspirin 325 mg, clopidogrel 600 mg as a loading dose, and a weight-adjusted unfractionated heparin regimen (bolus of 70 to 100 U/kg). The primary PCI was performed according to local institutional guidelines.

Patients received distal intracoronary administration of either of epinephrine 100 µgin in group I, verapamil 200 µg in group II, and nothing in Group III, via an over-the-wire balloon or a fenestrated monorail semi compliant balloon distal to the thrombus, just after passing the PTCA wire and before any further intervention.

Following the procedure, the patients received the standard regimen for STEMI including aspirin, clopidogrel, B-blockers, nitrates, low molecular weight heparin, angiotensinogen converting enzyme (ACE) inhibitors, diuretics, and calcium antagonists.

Study's outcomes

The primary endpoint in our study was the incidence of no-reflow, defined as a post-procedural TFG is < 3 or, in the case of a TFG of 3, when TMPG is 0 or 1. The secondary endpoints included major adverse cardiovascular and cerebrovascular events (MACCE) -described as in-hospital all-cause death, AMI, or ischemic stroke-, or peri-procedure complications.

Statistical analysis

The statistical software SPSS (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) was used for data processing and analysis. The central tendency and variability of the numerical data were presented in the form of mean ±standard deviations (SD) or median with interquartile range (IQR), according to the normality of data distribution. Categorical variables were summarized by frequency counts and percentages. The significance of association between study's interventions and study's outcomes was assessed using ANOVA test and Chi-square test for continuous and categorical data, respectively. P-value <0.05 was regarded as statistically significant.

Results

A total of 120 patients were randomized into one of the following three groups: group I who received distal intracoronary administration of epinephrine; group II who received verapamil; and group III who served as a control group. The mean age was 53.43 ± 9.88, 56.28 ± 9.10, 56.38 ± 10.05 in groups I,II and III respectively, and 80%, 80% and 77.5%, respectively, of them were males. The mean time to arrival to the hospital was 6.45 ± 3.47, 5 ± 3.2, 5.7 ± 2.7 hours, respectively, from maximal pain onset and they were transferred to the cardiac catheterization laboratory within a mean of 21.88 ± 6.58, 23.75 ± 4.44, 23.13 ± 5.67 minutes, respectively. There were no statistically significant differences between the studied groups for any of the baseline data (Table 1). The majority of group I patients showed single vessel disease

(67.5%), Left anterior descending coronary artery (LAD) was the most presented culprit vessel (67.5%) and 40% of the patients had type-C lesions, besides, 17 patients (42.5%) were TTG 5. Thrombus aspiration was done in 33 patients (82.5%) and pre-dilation in ten patients (25%). All patients received coronary stents with mean stent diameter of 3.28 ± 0.36 mm and length of 23.08 ± 6.69 mm. Group II and III patients showed similar characteristics with no statistically significant differences (Table 2). No serious arrhythmias or blood pressure alterations occurred in either group I or II (two instances of supraventricular and ventricular tachycardia occurred with epinephrine versus four instances of atrial fibrillation with verapamil. Hemodynamic parameters are shown in Table 2.

The angiographic flow and perfusion parameters were significantly improved in group I and II versus the control group, with better results in epinephrine group only TMPG3 was significantly higher with epinephrine (77.5%) than verapamil (55%) (p = 0.037) and TMPG2 was higher in verapamil (32.5%) than epinephrine (7.5%) (p = 0.003). No reflow is lower with epinephrine than verapamil (25% vs 27.5%); however, with no statistically significant difference (P=0.785) (Figure 1 and 2).

Group I showed ST-segment resolution in 33 (82.5%) patients within 90 minutes following reperfusion. Echocardiography was performed the following day with mean left-ventricular end-diastolic diameter (LVEDD) of 50.15 ± 3.8mm, left-ventricular end-systolic diameter (LVESD) of 40.15 ± 5.23mm, and ejection fraction (EF) of 46.85 ± 9.30%. These results were better than those seen with verapamil but, again, with no statistically significant difference (p>0.05). At 30th-day follow-up, a single (2.5%) patient in group I was hospitalized for heart failure but there are no major adverse cardiac events (MACE). Apart of this, no MACE happened for the three groups (Table 3).

Discussion

The prevention and treatment of no-reflow are critical; patients with the no-reflow phenomenon are the highest-risk subgroup of patients requiring reperfusion, with increased chances of early mortality and morbidity [17,18]. Ventricular arrhythmias and even heart failure have been attributed to the no-reflow phenomenon [19]. A research even shows that it could have a negative impact on left ventricular remodeling after AMI [20]. The no-reflow phenomenon has been linked to malignant arrhythmias, a lower ejection fraction, and a higher probability of cardiac death in follow-up trials [21]. Treatment of no-reflow improves myocardial perfusion, which can speed up the healing process by promoting functional regeneration of viable muscle, reducing infarct expansion [22]. In patients with acute MI, sufficient myocardial perfusion also increases survival [23].

A dedicated perfusion balloon, such as a Clearway balloon catheter, or a microcatheter, can be used to inject pharmacological agents into the coronary circulation [24]. Theoretically, this local injection results in higher receptor occupancy, a higher concentration of the administered agent, better bioavailability, and a longer residence period in the coronary vasculature [25]. In this study, our findings showed that both epinephrine and verapamil demonstrated a significant reduction in terms of heart rate and SBP, with no serious arrhythmias or BP alterations (p<0.001). Regarding flow and perfusion, while a significant improvement was observed in both groups (versus control) with better results in the epinephrine group; TMPG3 is significantly higher with epinephrine than verapamil (77.5% vs. 55%; p = 0.037, respectively), while TMPG2 was higher in verapamil than epinephrine (32.5% vs. 7.5%; p = 0.003, respectively). No-reflow was lower with epinephrine than verapamil (25% vs. 27.5%; p=0.78). No deaths or MACEs were recorded in this study.

Patients who experience refractory no-reflow following primary PCI for STEMI can benefit from intracoronary epinephrine, according to Aksu et al. [26]. Totally, about 75% of their included patients showed successful reversion of no-reflow after the administration of intracoronary epinephrine. They added that in 42% of the patients, the no-reflow phenomenon resulted in hypotension. All except one patient's hypotension was controlled after intracoronary epinephrine was administered. Similar to our

Table 1: Demographic and clinical characteristics of the studied population.

	Epinephrine	Verapamil	Control	p1	p2	p3
Age	53.43 ± 9.88	56.28 ± 9.10	56.38 ± 10.05	0.215	0.965	0.217
Male sex	32 (80%)	32 (80%)	31 (77.5%)	1.000	0.800	0.785
Smoking	32 (80%)	29 (72.5%)	28 (70%)	0.446	0.800	0.323
DM	14 (35%)	13 (32.5%)	17 (42.5%)	0.822	0.440	0.498
HTN	23 (57.5%)	24 (60%)	24 (60%)	0.800	1.000	0.800
DL	15 (37.5%)	15 (37.5%)	12 (30%)	1.000	0.446	0.474
FH	6 (15%)	11 (27.5%)	5 (12.5%)	0.200	0.110	0.743
PTD (min)	387.0 ± 208.69	301.5 ± 196.95	346.5 ± 166.22	0.083	0.234	0.370
DTB (min)	21.88 ± 6.58	23.75 ± 4.44	23.13 ± 5.67	0.109	0.580	0.372
Killip class						
1	28 (70%)	29 (72.5%)	32 (80%)	0.830	0.412	0.291
2	9 (22.5%)	7 (17.5%)	5 (12.5%)	0.623	0.534	0.291
3	3 (7.5%)	4 (10%)	3 (7.5%)	0.711	0.660	1.000

Continuous variables are expressed as mean ± SD while categorical variables as absolute and relative frequencies. p1-3, p-values for Group I vs II, II vs III, I vs III; DM, Diabetes mellitus; HTN, Hypertension; DL, Dyslipidemia; FH, Family history; PTD, Pain-to-door time; DTB, Door-to-balloon time.

Table 2: Baseline procedural characteristics of the studied population.

	Epinephrine	Verapamil	Control	p1	p2	p3
CAD extent						
1VD	27 (67.5%)	21 (52.5%)	28 (70%)	0.135	0.070	0.812
2VD	9 (22.5%)	10 (25%)	4 (10%)	0.800	0.110	0.168
3VD	4 (10%)	9 (22.5%)	8 (20%)	0.133	0.767	0.210
Culprit vessel						
LAD	27 (67.5%)	25 (62.5%)	25 (62.5%)	0.675	1.000	0.660
LCX	6 (15%)	4 (10%)	6 (15%)	0.534	0.486	1.000
RCA	7 (17.5%)	11 (27.5%)	9 (22.5%)	0.291	0.623	0.599
Lesion type						
A	12 (30%)	10 (25%)	10 (25%)	0.570	1.000	0.534
B	12 (30%)	11 (27.5%)	17 (42.5%)	0.812	0.160	0.256
C	16 (40%)	19 (47.5%)	13 (32.5%)	0.474	0.160	0.520
TTG						
0	0 (0%)	0 (0%)	0 (0%)	1.000	1.000	1.000
1	0 (0%)	0 (0%)	1 (2.5%)	1.000	0.323	0.323
2	2 (5%)	0 (0%)	2 (5%)	0.160	0.160	1.000
3	5 (12.5%)	2 (5%)	5 (12.5%)	0.183	0.262	1.000
4	16 (40%)	16 (40%)	15 (37.5%)	1.000	0.830	0.830
5	17 (42.5%)	22 (55%)	17 (42.5%)	0.256	0.281	1.000
TA	33 (82.5%)	38 (95%)	32 (80%)	0.058	0.057	0.785
PTCA	10 (25%)	17 (42.5%)	13 (32.5%)	0.147	0.421	0.474
Stenting	40 (100%)	40 (100%)	40 (100%)	1.000	1.000	1.000
Diameter	3.28 ± 0.36	3.21 ± 0.33	3.13 ± 0.31	0.317	0.275	0.078
Length	23.08 ± 6.69	22.53 ± 6.22	24.23 ± 5.44	0.734	0.169	0.366

Continuous variables are expressed as mean ± SD while categorical variables as absolute and relative frequencies. p1-3, p-values for Group I vs II, II vs III, I vs III; CAD, coronary artery disease; 1-3VD, single-three vessel disease; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; TTG, TIMI thrombus grade; TA, Thrombus aspiration; PTCA, percutaneous transluminal coronary angioplasty.

Table 3: In-hospital and 30days follow-up of the studied population.

	Epinephrine	Verapamil	Control	p1	p2	p3
STR	33 (82.5%)	32 (80%)	26 (65%)	0.785	0.160	0.070
LVEDD (mm)	50.15 ± 3.80	51.28 ± 3.29	50.03 ± 2.80	0.213	0.085	0.877
LVESD (mm)	40.15 ± 5.23	42.28 ± 3.28	41.43 ± 4.19	0.051	0.329	0.248
EF (%)	46.85 ± 9.30	43.85 ± 7.09	46.43 ± 7.84	0.128	0.147	0.833
TLR	0 (0%)	0 (0%)	0 (0%)	1.000	1.000	1.000
TVR	0 (0%)	0 (0%)	0 (0%)	1.000	1.000	1.000
MI	0 (0%)	0 (0%)	0 (0%)	1.000	1.000	1.000
Death	0 (0%)	0 (0%)	0 (0%)	1.000	1.000	1.000
Total MACE	0 (0%)	0 (0%)	0 (0%)	1.000	1.000	1.000
HF	1 (2.5%)	0 (0%)	0 (0%)	0.323	1.000	0.323

Continuous variables are expressed as mean ± SD while categorical variables as absolute and relative frequencies. p1-3, p-values for Group I vs II, II vs III, I vs III; STR, ST-segment resolution; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; EF, ejection fraction; MACE, major adverse cardiac event; TLR, target lesion revascularization; TVR, target vessel revascularization; MI, myocardial infarction; HF, heart failure.

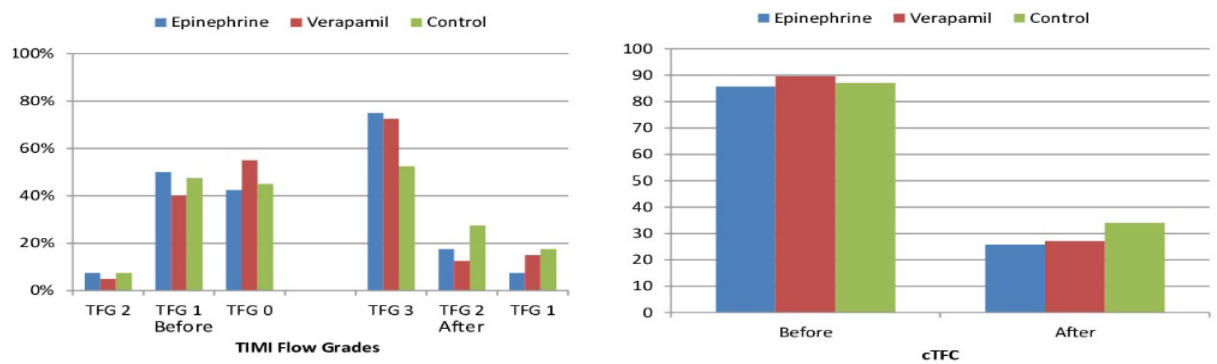

Figure 1: TIMI flow grade and corrected TIMI frame count before and after drug administration.

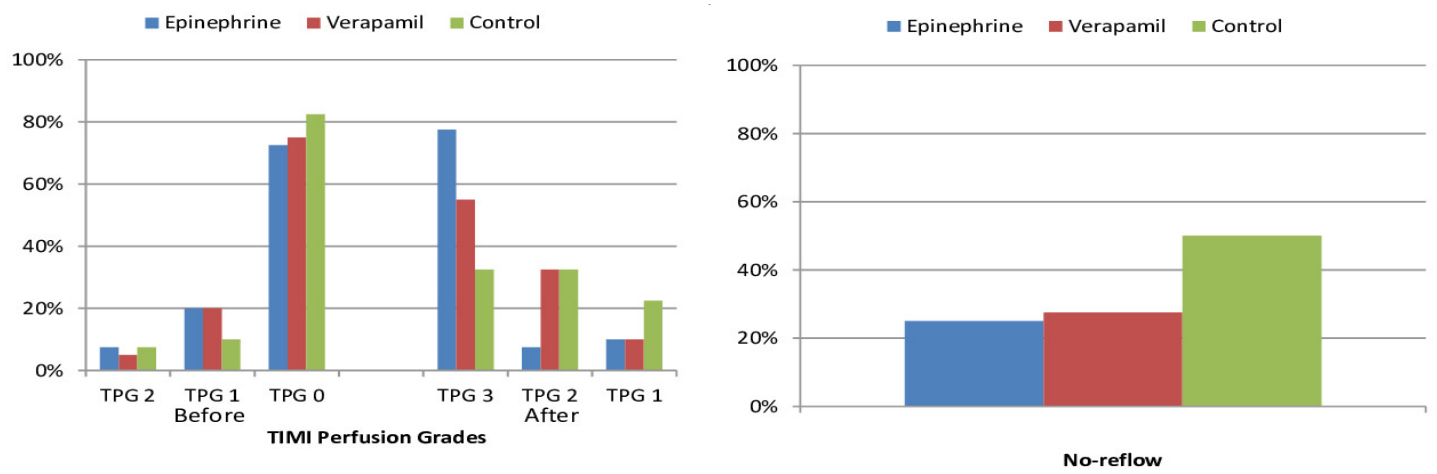

Figure 2: TIMI perfusion grades and no-reflow before and after drug administration.

findings, they did not record any deaths; however, one patient was hospitalized due to heart failure [26].

In the study of Skelding et al. [27], they found that TIMI 3 flow was developed in 69% of 29 patients with refractory no-reflow after administration of IC epinephrine. Likewise, there was a substantial but tolerable rise in heart rate with intracoronary epinephrine, but no reports of acute dysrhythmia in the study of Abu Arab and his colleagues [24]. Maluenda et al. [28] examined 30 patients with ACS who were complicated by no-reflow after PCI. Their findings showed a significant improvement in the TIMI flow in 63.3% of their patients after administering nitroprusside and in 53.3% in the nicardipine group, which translated into normal coronary flow at the end of the procedure. The rate of in-hospital death was 6.7% (2 cases).

A large network meta-analysis that evaluated the safety and efficacy of many agents, including diltiazem, adenosine, verapamil, nicorandil, and others, showed that adenosine was the best agent in terms of improving the myocardial reperfusion, clinical outcomes, and cardiac function [12]. Moreover, they found that there were no hypotension events or malignant arrythmia in the patients who received adenosine. According to their findings, verapamil was better than adenosine and the control agent regarding treatment efficacy for TFG<3. Further, verapamil ranked the second most effective agent after adenosine, according to the SUCRA analysis. Concerning the ST-segment resolution and LVEF, verapamil ranked fourth after adenosine, nicorandil, urapidil. On the other hand, the safety profile of verapamil was not encouraging, as it increased the risk of MACEs five times compared to adenosine (OR= 5.00, 95% Cl; 1.58 to 16.28).

In the meta-analysis conducted by Su et al. [29], verapamil significantly improved the TIMI myocardial perfusion grade (RR= 0.43, 95% CI; 0.29 to 0.64), reduced the incidence of no-reflow (RR= 0.33, 95% CI; 0.23 to 0.50), and decreased the TIMI frame count (MD= -11.62, 95% CI; -16.04 to -7.21). In terms of safety, they found a significant reduction in the MACEs during the hospitalization and after two months of follow-up (RR=0.37 and R=0.56, respectively). There were no malignant ventricular arrhythmias or hemodynamic anomalies found in the Taniyama 1997 study after verapamil was given, and the number of patients with TIMI flow grade 3 decreased from six to three [30].

In the study of Fu et al. [31], they reported that administration of verapamil was resulted in reversing of the no-reflow in 84% of the participants; however, two patients developed transient hypotension, which resolved spontaneously after three minutes. They also showed that three patients showed sinus bradycardia; there was a transient type II sinoatrial block in one patient, and one patient developed type I atrioventricular block. All adverse effects were alleviated after intravenous injection of atropine (0.5–1 mg).

To the best of our knowledge, this is the first study that compared epinephrine and verapamil in terms of the safety and efficacy in managing the no-reflow phenomenon after during PPCIs. However, our study has some limitations, including the small sample size, the relatively short follow-up period and single center study.

In conclusion, the current evidence suggests that epinephrine and verapamil are safe and effective in managing patients with no-reflow during PPCIs. Further studies with a larger sample and a longer duration of follow-up are required to confirm these findings.

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