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***Original research article***

# COMPARATIVE EFFICACY OF INTRACORONARY VERAPAMIL AND ADRENALINE IN MANAGING CORONARY NO-REFLOW DURING PRIMARY PCI IN STEMI PATIENTS AT A TERTIARY CARE HOSPITAL

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**Abstract:** *Coronary No-Reflow (CNR) is a significant complication during Primary Percutaneous Coronary Intervention (PPCI) for ST-Elevation Myocardial Infarction (STEMI), often leading to poor clinical outcomes. Management strategies for CNR include various pharmacological agents, among which intracoronary verapamil and intracoronary adrenaline are commonly used alongside Glycoprotein IIb/IIIa inhibitors.* ***Objective:*** *This study aims to compare the effectiveness of intracoronary verapamil versus intracoronary adrenaline, alongside Glycoprotein IIb/IIIa inhibitors, in managing Coronary No-Reflow (CNR) during Primary Percutaneous Coronary Intervention (PPC1) for STEMI patients.* ***Methodology:*** *This randomized-control-trial was conducted at the Department of Cardiology, MTI Lady Reading Hospital Peshawar, Pakistan, from May 2023 to April 2024. Fifty patients diagnosed with CNR during PPC1 were randomised into two groups: adrenaline and verapamil. The primary outcome measures were TIMI Flow Grade (TFG) and Myocardial Blush Grade (MBG) immediately post-intervention. In contrast, secondary outcomes included Major Adverse Cardiovascular Events (MACE), myocardial infarction, stroke, target vessel revascularisation, mortality, and Left Ventricular Ejection Fraction (LVEF) assessed at baseline and one-month follow-up. Statistical analyses were performed using IBM SPSS version 20, with significance at $P<0.05$.* ***Results:*** *Baseline characteristics, procedural details, and initial TIMI flow grades were similar between groups. Adrenaline achieved universal TIMI 3 flow compared to 84% with verapamil ($p=0.049$), but no significant differences were noted in myocardial blush grades. Adrenaline led to significantly higher follow-up LVEF ($45.0 \pm 9.0$ vs. $39.0 \pm 9.0$, $p=0.027$) and a more significant percentage change in LVEF (20.97% vs. 8.94%, $p=0.042$) than verapamil. Adverse event rates were comparable except for lower MACE incidence at 30 days with adrenaline (8.0% vs. 24.0%, $p=0.039$).* ***Conclusion:*** *Adrenaline notably enhanced TIMI 3 flow rates, improved left ventricular ejection fraction, and decreased significant adverse cardiovascular events at 30 days compared to verapamil. These findings suggest that adrenaline may be a superior option for improving coronary blood flow and early clinical outcomes in this patient population.*

**Keywords:** Adrenaline, Verapamil, Myocardial infarction, Coronary No-reflow, TIMI, MBG.

## Introduction

ST-segment elevation myocardial infarction (STEM1) is primarily caused by the complete thrombotic blockage of one or more epicardial coronary arteries. (1) Current clinical trials and guidelines highlight the crucial role of rapid and effective myocardial reperfusion through primary percutaneous coronary intervention (PPCI) to lower major adverse cardiac events (MACE) and mortality rates. (2) A notable complication during PPCI is coronary no-reflow (CNR), which negatively impacts both short-term and long-term outcomes. (3, 4)

CNR is characterised by reduced coronary flow and myocardial perfusion despite reperfusion therapy with PCI during acute myocardial infarction (MI). (4) This condition is identified immediately post-PCI when the angiographic Thrombolysis in Myocardial Infarction (TIMI) flow score is less than three or if the TIMI flow is three. Still, the Myocardial Blush Grade (MBG) is 0 or 1, or when ST-segment resolution is less than 70% within 60-90 minutes after the procedure. (5, 6)

The exact pathophysiology of CNR remains incompletely understood, leading to uncertainties about the best treatment strategies. (4) Current STEM1 management guidelines primarily advocate for GP IIb/IIIa inhibitors. (7) Other proposed treatments, including mechanical interventions like balloon inflation or thrombus aspiration and pharmacological agents such as intracoronary adenosine, sodium nitroprusside, nitrates, verapamil, and adrenaline, have not been accepted universally. (8)

This study aims to assess the efficacy and safety of intracoronary adrenaline compared to traditional treatments in STEM1 patients experiencing refractory CNR during primary PCI. The findings could also guide future research on using intracoronary adrenaline in other clinical settings, such as elective PCI or acute coronary syndromes, providing deeper insights into the mechanisms and optimal management of no-reflow phenomena. Thus, this study aims to compare the effectiveness of intracoronary verapamil versus intracoronary adrenaline, alongside Glycoprotein IIb/IIIa inhibitors, in managing CNR during primary PCI for STEMI patients.

## Methodology

This study utilised a single-centre randomised controlled trial design, accomplished at the Department of Cardiology,

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MTI Lady Reading Hospital Peshawar, Pakistan, from May 2023 to April 2024. The research proposal received approval from the institute's ethical committee. The study included all patients presenting with ST-segment elevation myocardial infarction (STEMI) who developed Coronary No-flow (CNR) during Primary Percutaneous Coronary Intervention (PPCI).

Informed consent was obtained from all participants after detailed information was collected, including demographics (name, age, sex, race), clinical history (smoking status, diabetes, hypertension), renal function, history of coronary artery disease, previous coronary interventions, and time to first medical contact. Vital signs and a 12-lead ECG were documented within 10 minutes of arrival. Upon diagnosis of STEMI, patients underwent PPCI performed by experienced interventional cardiologists conducting more than 75 procedures annually.

The inclusion criteria encompassed patients who were 18 years or older and met the diagnostic criteria for STEMI, evidenced by persistent chest pain and ECG findings indicative of ST-segment elevation. Patients were eligible if they developed CNR during PPCI despite successful epicardial vessel revascularisation.

Exclusion criteria included patients requiring rescue PCI following thrombolysis, those experiencing procedural complications such as dissection or mechanical complications, individuals with significant multi-vessel disease, contraindications to adrenaline (e.g., severe hypertension, allergy), contraindications to verapamil (e.g., severe hypotension, cardiogenic shock), and patients who received both study medications.

Diagnostic coronary angiography was performed to visualise coronary anatomy and identify culprit vessels—all PPC1 procedures adhered to current guidelines, utilising Drug-Eluting Stents (DES) based on operator discretion.

Patients diagnosed with CNR (n=50) were randomly assigned using a computer-generated randomisation program into two equal groups (n=25 per group): Group A (adrenaline group) and Group B (verapamil group). Group A received a loading dose of tirofiban (0.25 mg/kg) followed by 200 micrograms of intracoronary adrenaline administered distal to the lesion via a microcatheter. Group B received the same tirofiban loading dose followed by 200 micrograms of intracoronary verapamil.

The main objective was to evaluate the resolution of no-reflow using TIMI Flow Grade (TFG) and Myocardial Blush Grade (MBG) immediately after the intervention as the primary outcome. Secondary outcomes included Major Adverse Cardiovascular Events (MACE), incidence of myocardial infarction, stroke, target vessel revascularisation, mortality, and echocardiographic assessment of Left Ventricular Ejection Fraction (LVEF) at baseline and one-month follow-up.

The statistical analysis was carried out utilising IBM SPSS version 20. Descriptive statistics were used for qualitative and quantitative data presentation, with Chi-square and Fisher's tests employed for comparative analyses among both treatment groups. Statistical significance was defined as $P<0.05$ for all analyses conducted.

**Results**

In this study comparing intracoronary adrenaline to intracoronary verapamil for managing no-reflow during primary percutaneous coronary intervention (PPCI) in STEMI patients, 50 participants were enrolled, with 25 in each treatment group. The baseline clinical characteristics were relatively the same in both subgroups. The mean age was 58± 9.0 years in the adrenaline group and 56.5± 10.0 years in the verapamil group. Most participants were male (80.0% in the adrenaline group and 72.0% in the verapamil group). Common comorbidities included diabetes (40.0% vs. 48.0%), hypertension (60.0% vs. 56.0%), and smoking history (72.0% vs. 64.0%), with similar distributions between groups (Figure 1).

Regarding procedural characteristics, door-to-balloon time they averaged 68.5± 12.0 minutes for the adrenaline group and 70.0± 13.0 minutes for the verapamil group, with no significant difference observed. The distribution of infarct-related arteries (left anterior descending, left circumflex, and right coronary artery) and the TIMI flow grades before intervention (0 or 1) were comparable between groups, indicating consistency in baseline cardiac anatomy and severity of ischemia (Table 01).

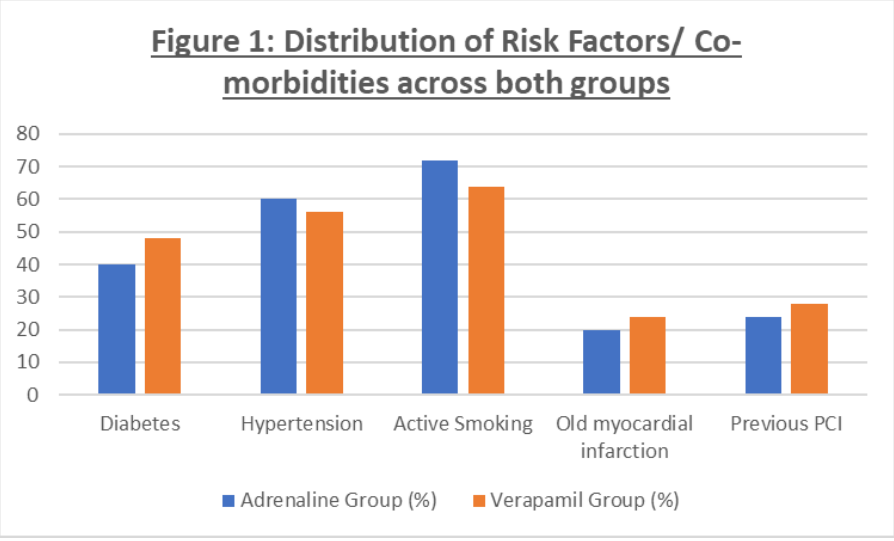


**Figure 1: Distribution of risk factors among study population**

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**Table 01: Baseline Variables of the two study groups**

| Variables | | I/C Adrenaline Group (n=25) | I/C Verapamil Group (n=25) | p-value* |
|---|---|---|---|---|
| Age(years), mean ± SD | | 58.0 ± 9.0 | 56.5 ± 10.0 | N/S |
| Gender, n (%) | Males | 20 (80.0%) | 18 (72.0%) | N/S |
| | Female | 5 (20.0%) | 7 (28.0%) | N/S |
| Body mass index(kg/m²), mean ±SD | | 26.5 ± 3.5 | 27.0 ± 3.8 | N/S |
| **Risk Factors/ Co-morbidities** | | | | |
| Diabetes, n (%) | | 10 (40.0%) | 12 (48.0%) | N/S |
| Hypertension, n (%) | | 15 (60.0%) | 14 (56.0%) | N/S |
| Active Smoking, n (%) | | 18 (72.0%) | 16 (64.0%) | N/S |
| Old myocardial infarction, n (%) | | 5 (20.0%) | 6 (24.0%) | N/S |
| Previous PCI, n (%) | | 6 (24.0%) | 7 (28.0%) | N/S |
| Door-to-balloon time (min), mean ±SD | | 68.5 ± 12.0 | 70.0 ± 13.0 | N/S |
| **Infarct-related artery, n (%)** | | | | |
| Left anterior descending | | 9 (36.0%) | 8 (32.0%) | N/S |
| Left circumflex | | 4 (16.0%) | 5 (20.0%) | N/S |
| Right coronary artery | | 12 (48.0%) | 12 (48.0%) | N/S |
| **TIMI flow before intervention, n (%)** | | | | |
| TIMI-0 | | 10 (40.0%) | 9 (36.0%) | N/S |
| TIMI-1 | | 15 (60.0%) | 16 (64.0%) | N/S |
| Total time of ischemia (min), mean ± SD | | 206.0 ± 40.0 | 210.0 ± 42.0 | N/S |

*N/S=Not-significant(p >0.05)

Table 02 outlines the primary outcomes comparing two treatment groups. The study assessed thrombolysis in myocardial infarction (TIMI) flow and myocardial blush grades (MBG) post-intervention. TIMI 2 flow was absent in the Adrenaline group but present in 16% of the Verapamil group. TIMI 3 flow was achieved universally in the Adrenaline group and in 84% of the Verapamil group, showing statistical significance (p=0.049). However, there were no notable differences in MBG 0-1 (Adrenaline 40%, Verapamil 60%) or MBG 2-3 (Adrenaline 60%, Verapamil 40%), with a p-value of 0.175, indicating similar myocardial perfusion outcomes between the groups based on MBG.

**Table 02: Primary Outcomes Post-intervention according to TFG and MBG**

| Primary Outcomes | I/C Adrenaline Group (n=25) | I/C Verapamil Group (n=25) | p-value | Significance |
|---|---|---|---|---|
| TIMI flow Grade(TFG) | | | | |
| TIMI-2 | 0 (0.00%) | 4 (16.00%) | 0.049 | Significant |
| TIMI-3 | 25 (100.00%) | 21 (84.00%) | | |
| Myocardial Blush Grade(MBG) | | | | |
| MBG 0-1 | 10 (40.00%) | 15 (60.00%) | 0.175 | Not significant |
| MBG 2-3 | 15 (60.00%) | 10 (40.00%) | | |

The study also evaluated left ventricular ejection fraction (LVEF) at index and follow-up and the percentage change in LVEF after treatment. The mean index LVEF was 37.2 ± 8.3 in the Adrenaline group and 35.8 ±8.1 in the Verapamil group, showing no significant difference (p=0.684). However, at follow-up, the Adrenaline group had a significantly higher mean LVEF of 45.0 ± 9.0 compared to 39.0 ± 9.0 in the Verapamil group (p=0.027). The percentage change in LVEF was also considerably higher in the Adrenaline group (20.97 ± 28.5%) compared to the Verapamil group (8.94 ± 18.2%), with a p-value of 0.042, indicating a better improvement in LVEF with adrenaline treatment, outlined in table 03.

**Table 03: LVEF Assessment and Outcome at One-month Follow-up**

| Secondary Outcome of LVEF | I/C Adrenaline Group(n=25) | I/C Verapamil Group(n=25) | p-value | Significance |
|---|---|---|---|---|
| Index LVEF, Mean ±SD | 37.2 ± 8.3 | 35.8 ± 8.1 | 0.684 | Non-significant |
| Follow-up LVEF, Mean ±SD | 45.0 ± 9.0 | 39.0 ± 9.0 | 0.027 | Significant |
| % Change in LVEF, Mean ± SD | 20.97 ± 28.5 | 8.94 ± 18.2 | 0.042 | Significant |

Table 04 presents the secondary outcomes comparing the Intracoronary (I/C) Adrenaline group and 1/C Verapamil group, each comprising 25 participants. The study aimed to compare the occurrence of myocardial infarction, stroke, target vessel revascularisation, major adverse cardiovascular events (MACE) at 30 days, and mortality between the two study groups. Results indicated that myocardial infarction rates were 4.0% in the Adrenaline group and 8.0% in the Verapamil group, showing no statistical significance (p=Not Significant). No cases of stroke were reported in either group. Target vessel revascularisation rates were 4.0% in the Adrenaline group and 16.0% in the Verapamil group, which was also not statistically significant. However, the incidence of MACE

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at 30 days was significantly lower in the Adrenaline group (8.0%) compared to the Verapamil group (24.0%), with a p-value of 0.039, indicating a favourable trend suggesting adrenaline's potential in reducing adverse cardiovascular events within the first-month post-intervention. There were no reported deaths in either group during the study period.

**Table 04: Secondary Outcomes at One-Month Follow-up**

| Secondary Outcome(s) | I/C Adrenaline Group (n=25) | I/C Verapamil Group (n=25) | p-value* |
|---|---|---|---|
| Myocardial infarction, n (%) | 1 (4.0%) | 2 (8.0%) | N/S |
| Stroke, n(%) | 0 (0%) | 0 (0%) | N/S |
| Target vessel revascularisation, n (%) | 1 (4.0%) | 4 (16.0%) | N/S |
| Major adverse cardiovascular events at 30 days, n (%) | 2 (8.0%) | 6 (24.0%) | 0.039 |
| Death, n (%) | 0 (0%) | 0 (0%) | N/S |

**N/S=Not-significant(p >0.05)*

**Discussion**

Our research sought to assess the effectiveness of intracoronary adrenaline compared to intracoronary verapamil in addressing the no-reflow phenomenon during primary percutaneous coronary intervention (PPCI) among STEMI patients. Our findings indicated notable distinctions between these treatments, emphasising their strengths and weaknesses. Our findings showed that intracoronary adrenaline led to superior outcomes in achieving TIMI 3 flow, with 100% of patients in the adrenaline group reaching this grade, compared to 84% in the verapamil group. This aligns with the study by Khan et al., which reported higher intracoronary adrenaline efficacy than adenosine in resolving the no-reflow phenomenon.(9) Additionally, the significant difference in TIMI 2 flow, with no instances in the adrenaline group versus 16% in the verapamil group (p=0.049), underscores adrenaline's rapid and effective action in improving immediate coronary blood flow. However, no substantial differences were found between the two groups when assessing myocardial blush grade (MBG). The MBG results suggest that while adrenaline effectively enhances macrovascular flow (TIMI grades), its impact on microvascular perfusion (MBG) may not be significantly superior to verapamil. This finding contrasts with the observations by Yassin et al., who found a higher efficacy of intracoronary adrenaline in preventing no-reflow during PPC1 compared to verapamil. (10)

The study also examined changes in left ventricular ejection fraction (LVEF). While the initial LVEF was comparable between the groups, the follow-up LVEF showed a statistically significant increase in the adrenaline group (45.0 ± 9.0) compared to the verapamil group (39.0 ± 9.0) (p=0.027). Additionally, the percentage change in LVEF was significantly higher with adrenaline (20.97 ± 28.5%) than with verapamil (8.94 ± 18.2%) (p=0.042). This substantial enhancement in LVEF with adrenaline treatment aligns with the observations of Skelding et al., who first documented the effectiveness and safety of intracoronary adrenaline in managing refractory no-reflow. (11)

Regarding secondary outcomes, our study showed a considerably lower incidence of major adverse cardiovascular events (MACE) at 30 days in the adrenaline group (8.0%) compared to the verapamil group (24.0%) (p=0.039). This finding suggests that adrenaline improves immediate coronary blood flow and contributes to better early clinical outcomes. This result is in line with the studies by Navarese et al. and Hochholzer et al., which underlined the efficacy of intracoronary adrenaline in reducing adverse cardiovascular events. (12, 13)

Intracoronary adrenaline in our study demonstrated significant improvements in both primary and secondary outcomes, supporting its role as a potent agent in managing no-reflow during PPCI. Our findings concur with those of Khan et al., who reported higher efficacy and safety of intracoronary adrenaline than adenosine. (9) Conversely, the results differ from those of Hafez et al., who suggested that verapamil might be superior to adrenaline. (14) These discrepancies could be attributed to differences in study designs, patient populations, and methodologies.

Overall, our study contributes substantial evidence endorsing the utilisation of intracoronary adrenaline for managing no-reflow in STEM1 patients undergoing PPCI, highlighting notable improvements in coronary blood flow and early clinical outcomes. Further investigations, particularly large-scale randomised controlled trials, are essential to validate these findings and effectively refine treatment protocols to address the no-reflow phenomenon.

**Conclusion**

This study illustrates that intracoronary adrenaline surpasses verapamil in managing no-reflow during primary percutaneous coronary intervention in STEMI patients. Adrenaline notably enhanced TIMI 3 flow rates, improved left ventricular ejection fraction and decreased significant adverse cardiovascular events at 30 days compared to verapamil. These findings suggest that adrenaline may be a superior option for improving coronary blood flow and early clinical outcomes in this patient population. Further research is needed to confirm these results and optimise treatment protocols.

**Declarations**

**Data Availability statement**

All data generated or analysed during the study are included in the manuscript.

**Ethics approval and consent to participate.**

Approved by the department concerned. (IRB/MIT-415 dated 11-2-22)

**Consent for publication**

Approved

**Funding**

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**Conflict of interest**

The authors declared an absence of conflict of interest.

**Authors Contribution**

***SAJJAD KHAN (Fellow Interventional Cardiology)***
*Final Approval of version*
***SAMI UR REHMAN (Fellow Interventional Cardiology)***
*Revisiting Critically*
***WASIM SAJJAD (Fellow Interventional Cardiology) & SUMERA BEGUM (Senior Registrar)***
*Data Analysis*
***REHANA YASMIN (Final Year MBBS) & IKRAM ULLAH ADIL (Assistant Professor)***
*Drafting & Concept & Design of Study*

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