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EFFICACY OF INTRACORONARY ADENOSINE AND VERAPAMIL IN NO-REFLOW AMONG NORMOTENSIVE PATIENTS PRESENTING WITH ACUTE CORONARY SYNDROME

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ABSTRACT

Objective: To compare the efficacy of intracoronary adenosine and verapamil in improving myocardial perfusion in normotensive patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI).

Study Design: This was a prospective observational study.

Place and Duration: This study was conducted at Chandka Medical College Hospital Larkana, while the cath procedures were performed at (SICVD) Larkana from February 2025 to February 2026.

Methods: A total of 120 normotensive patients with ACS undergoing PCI were enrolled and equally allocated into 2 groups. The adenosine group (n=60) received intracoronary adenosine, while the verapamil group (n=60) received intracoronary verapamil. Post-procedural Thrombolysis in Myocardial Infarction (TIMI) flow grade was the primary outcome variable. Secondary outcomes included a 6-month major adverse cardiac events (MACE), Index of Microcirculatory Resistance (IMR), and flow-mediated dilatation (FMD). Independent-samples t-test and chi-square test were used for analysis, with $p<0.05$ considered significant.

Results: Baseline variables were comparable between groups. Mean age was 60.0 ± 7.0 years in the adenosine group and 58.0 ± 6.0 years in the verapamil group (p=0.34). Male participants accounted for 48.3% and 53.3%, respectively (p=0.57). Post-treatment TIMI flow was significantly higher in the verapamil group than in the adenosine group (2.9 ± 0.4 vs 2.6 ± 0.5, p=0.02). Post-procedural IMR was lower in the adenosine group (18.0 ± 2.0 vs 20.0 ± 3.0, p=0.08), while post-procedural FMD was higher in the verapamil group (4.3 ± 0.6 vs 4.0 ± 0.7, p=0.12). At 6 months, MACE was lower in the adenosine group (11.7% vs 23.3%, p>0.05).

Conclusion: Intracoronary verapamil showed superior immediate improvement in TIMI flow, while adenosine demonstrated a favorable trend in IMR and lower 6-month MACE. However, neither drug was consistently superior across all outcomes.

Keywords: Acute Coronary Syndrome, No-Reflow Phenomenon, Intracoronary Adenosine, Intracoronary Verapamil, Percutaneous Coronary Intervention.

INTRODUCTION

Acute coronary syndrome (ACS) is a set of disorders caused by an abrupt drop in coronary blood flow that results in myocardial ischemia. This range encompasses unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) [1]. The recommended therapy for the majority of ACS patients, particularly those with STEMI or high-risk NSTEMI, is percutaneous coronary intervention (PCI) to restore blood flow [2]. Nevertheless, the successful opening of the culprit vessel does not necessarily result in effective myocardial perfusion, which can lead to the no-reflow phenomenon [3]. Angiographically, this is defined as a permanent myocardial dysperfusion (TIMI flow grade ≤2 or myocardial blush grade <2)

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due to the coronary microcirculation, even though PCI restores the epicardial coronary flow [4].

In the literature, no-reflow is increasingly being discussed as a predictable phenomenon in identified high-risk patients rather than a causal complication [3]. Its occurrence has lately been attributed to excessive thrombus burden, prolonged ischemic time, long lesion length, poor left-ventricular function, inflammatory stimulation, and other prothrombotic factors, including increased D-dimer [5]. Imaging has further clarified the presence of lipid-rich, thin-cap fibroatheroma-type plaques, which are more likely to embolize at the distal end and cause microvascular blockage during PCI. This is significant because the no-reflow mechanism of ACS differs: in some patients, thrombotic embolization is the predominant mechanism, whereas in others, vasomotor dysfunction or reperfusion injury is more typical [3, 6].

Adenosine and verapamil are commonly used as intracoronary pharmacologic agents because both reverse reversible microvascular dysfunction via distinct physiological mechanisms. Adenosine is mainly linked to vasodilation via A2A receptors, platelet inhibition, and ischemic preconditioning, and its short half-life limits its systemic actions [7, 8]. However, verapamil, a non-dihydropyridine calcium-channel blocker, inhibits calcium-dependent vasoconstriction and could be more effective against microvascular spasm [8, 9]. Yet, the data on the effectiveness of adenosine and verapamil remain incomplete. According to a meta-analysis focusing on primary PCI no-reflow, Verapamil was significantly associated with the attainment of a final TIMI grade 3 and over 70% ST-segment resolution, in contrast to adenosine, which provided only a marginal benefit in ST-resolution but did not exhibit a significant improvement in TIMI 3 [10]. Both agents had no effect on MACE or mortality, which were underpowered, but verapamil had the highest angiographic success rate [10]. Another study of comparison between adenosine and combined epinephrine/verapamil in STEMI no-reflow further showed equivalent primary endpoint achievement between pharmacologic classes when delivered distally via microcatheter [7].

Even though both adenosine and verapamil are widely used in no-reflow, there is little evidence comparing the two drugs in normotensive ACS patients directly. This leaves uncertainty about which agent offers more reliable restoration of coronary flow in a clinically common subgroup where blood pressure preservation is especially relevant during intracoronary vasodilator therapy. Therefore, the current research's aim is to compare intracoronary adenosine and verapamil for the management of no-reflow in normotensive patients with ACS undergoing PCI.

METHODOLOGY

This research compared the effectiveness of verapamil and intracoronary adenosine in recovering myocardial perfusion during PCI in normotensive individuals with ACS. This research set out to quantify the degree to which TIMI flow grade improved both immediately after and 30 minutes following the intervention. 120 qualified patients were recruited and randomly allocated to two groups: 60 to intracoronary adenosine and 60 to intracoronary verapamil.

Adult patients aged 18 or more years with ACS and receiving PCI were the participants in the current research. In the current study, participants with systolic and diastolic blood pressure of 120 to 130 mmHg and 85 to 80 mmHg during the procedure were recruited as normotensive patients. The exclusion criteria included a history of allergy or contraindication with verapamil or adenosine, cardiogenic shock, hemodynamic instability, chronic renal failure (serum creatinine >1.5 mg/dL), and past coronary artery bypass graft surgery. The research obtained written consent from all participants prior to the study.

Clinical information was derived using hospital records, procedure documentation, and post-discharge evaluations. The outcome variable was primarily myocardial reperfusion, measured using TIMI flow grade on coronary angiography. Endpoints were secondary: endothelial function, assessed by brachial artery flow-mediated dilation (FMD) and the Index of Microcirculatory Resistance (IMR), measured using a pressure-wire system before and after PCI. A six-month follow-up was done to monitor major adverse cardiac events (MACE), including repeat revascularization, death and non-fatal myocardial infarction.

To perform statistical analysis, SPSS 25.0 was used. The results were reported as means with standard deviations, whereas categorical variables were compared using the chi-square test. A p-value of <0.05 was considered statistically significant. The independent-samples t-test was also applied.

RESULTS

The study involved 120 patients, 60 in the adenosine group, and 60 in the verapamil group. The number of male participants was marginally higher in the verapamil group (n=32, 53.3%) than in the adenosine group (n=29, 48.3%; p=0.57). The mean age was 60.0 ± 7.0 years in the adenosine group and 58.0 ± 6.0 years in the verapamil group (p=0.34). Baseline TIMI flow was 2.2 ± 0.7 versus 2.0 ± 0.6 (p=0.39). Pre-procedural IMR was 28.0 ± 5.0 and 30.0 ± 4.0 units (p=0.26), while FMD was 3.4 ± 0.5% and 3.1 ± 0.4% (p=0.22) (Table 1).

Table 1: Demographic And Clinical Profile Of Participants At Baseline (N=120)

Variable	Adenosine (n = 60)	Verapamil (n = 60)	p-value
Age (years)	60.0 ± 7.0	58.0 ± 6.0	0.34
Sex (% Male)	49.0%	54.0%	0.57
IMR Pre (units)	28.0 ± 5.0	30.0 ± 4.0	0.26
FMD Pre (%)	3.4 ± 0.5	2.9 ± 0.4	0.22
Baseline TIMI	2.2 ± 0.7	2.0 ± 0.6	0.39

Post-PCI outcomes were comparatively better in the verapamil group. Post-treatment TIMI was higher with verapamil than adenosine (2.9 ± 0.4 vs 2.6 ± 0.5, p=0.02), showing a statistically significant difference. In the verapamil group, IMR post-intervention was higher than in the adenosine group (20.0 ± 3.0 vs 18.0 ± 2.0, p=0.08), though this difference was not statistically significant. Similarly, FMD post-intervention was also greater in the verapamil group (4.3 ± 0.6 vs 4.0 ± 0.7, p=0.12), showing a non-significant statistical difference (Table 2).

Table 2: Comparison Of Post-Intervention Microvascular And Endothelial Outcomes Between Both Groups

Outcome	Adenosine (n = 60)	Verapamil (n = 60)	p-value
FMD Post (%)	4.0 ± 0.7	4.3 ± 0.6	0.12
Post-Treatment TIMI	2.6 ± 0.5	2.9 ± 0.4	0.02
IMR Post (units)	18.0 ± 2.0	20.0 ± 3.0	0.08

Fewer MACE were observed in the adenosine group at the 6-month follow-up (n=7, 11.7%) compared to the verapamil group (n=14, 23.3%). Despite this, no significant difference was observed (p>0.05), indicating that both groups showed comparable longer-term safety outcomes despite the numerically higher event rate in the verapamil group (Table 3).

Table 3: Comparison of Six-Month MACE Between the Study Groups

Outcome	Adenosine (n = 60)	Verapamil (n = 60)	p-value
MACE at 6 months, n (%)	7 (11.7%)	14 (23.3%)	>0.05

DISCUSSION

This study compared intracoronary adenosine and intracoronary verapamil for the treatment of no-reflow during PCI in patients with ACS. The first important finding is that the two groups were broadly comparable at baseline. The post-treatment TIMI flow in verapamil group was found to be significantly higher than in adenosine group. This suggests that verapamil may have been more effective in restoring immediate epicardial coronary flow after no-reflow occurred. This result aligns closely with a study by Soomro et al., which similarly reported statistically significant improvement in TIMI flow grades with verapamil over adenosine [11]. Arab et al. also reported that intracoronary vasoactive therapy improved final reperfusion and highlighted verapamil as one of the effective rescue options [7]. Moreover, Oliveri et al. found that, among pharmacologic interventions used in no-reflow during primary PCI, verapamil was associated with increased odds of final TIMI grade 3 flow compared with control [10].

Despite the fact that the difference was not statistically significant, our study demonstrated that the adenosine group exhibited a lower post-procedural IMR than the verapamil group. This means that although verapamil looked better on TIMI flow, adenosine may still have shown a favorable microvascular physiological signal. This comparison aligns with a randomized, triple-blind, placebo-controlled trial of STEMI patients undergoing primary PCI, in which intracoronary adenosine did not meaningfully reduce angiographic no-reflow relative to placebo but was associated with a much higher recovery in left ventricular ejection fraction at 40 days. This trial indicates that adenosine may not be required to enhance immediate angiographic outcomes, but may have downstream effects on myocardial or microvascular recovery [12].

The FMD outcomes also support the idea that reperfusion is multidimensional. Post-procedural FMD was greater in the verapamil group in the current study, although the difference was not statistically significant. This suggests that verapamil might have had some endothelial benefits, though not robust enough to establish clear superiority [8, 9]. Borzuta et al. underline that no-reflow is not dictated by a single process; it is a complex of distal embolization, ischemia-reperfusion injury, endothelial dysfunction, inflammatory plugging, and microvascular spasm [13]. Because of that complexity, one agent may improve one endpoint while another performs better on a different endpoint [13]. This is what our results demonstrate. Verapamil was better on TIMI and numerically

better on FMD, whereas adenosine showed a numerically lower IMR. Therefore, the current results are more consistent with current world knowledge that no-reflow therapies cannot be evaluated using a single reperfusion measure but require a combination of multiple reperfusion markers [14].

The adenosine group (11.7%) had fewer MACE than the verapamil group (23.3%) at the 6-month follow-up, but these differences were not statistically significant. This is in line with the study by Bendary et al., which concluded that all medications were equivalent with respect to composite events and that the verapamil, adenosine, and epinephrine groups had no significant difference in three-month MACE rates relative to control [15]. Our results differ from those reported by Darwish et al., who compared epinephrine to adenosine in refractory no-reflow and found significantly higher one-year MACE with adenosine (26.7% versus 11.3%, $p<0.01$), and were strongly influenced by heart-failure events [16]. In addition, Tahirkheli et al. documented low one-year MACE (8.7%) and low slow/no-reflow rates, suggesting that adenosine protocols can achieve long-lasting results even in complex anatomy [17]. Our findings revealed that no-reflow management cannot be based on a single outcome measure of intracoronary therapies. The results also suggest that no drug can be declared universally superior based on the current data, and more extensive comparative trials are required before one agent can be deemed superior to the other across all outcomes.

This study was conducted in a relatively small sample from a single clinical setting, which may limit the generalizability of the findings. In addition, the observational design and short follow-up period may have reduced the ability to detect causal differences and longer-term outcome variations between the two treatment groups. Lastly, the six-month observation period was limited and may have been insufficient to detect delayed clinical events or longer-term differences in outcomes related to the two intracoronary treatment strategies.

CONCLUSION

Intracoronary verapamil demonstrated greater improvement in post-treatment TIMI flow than adenosine, suggesting a stronger effect on immediate angiographic reperfusion. Nonetheless, there was no significant difference between the groups in post-procedural IMR, FMD, or 6-month MACE, indicating that neither agent demonstrated superiority across all outcome measures. These results indicate that adenosine and verapamil might affect multiple aspects of the no-reflow phenomenon rather than producing a consistent treatment effect. Future multicenter studies with larger sample sizes, extended follow-up, and more in-depth microvascular assessment are needed to further clarify their relative safety and efficacy in normotensive ACS patients undergoing PCI.

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