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Title: **Effects of Preloading with High Dose of Atorvastatin Prior to Percutaneous Coronary Intervention: A Single Center Randomized Controlled Trial**

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Effects of Preloading with High Dose of Atorvastatin Prior to Percutaneous Coronary Intervention: A Single Center Randomized Controlled Trial

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ABSTRACT

Background. Percutaneous coronary intervention (PCI) establishes the blood flow back to the heart. However, it can damage myocardium, leading to various cardiovascular events. Atorvastatin have beneficial pleiotropic cardiovascular effects, in addition to their lipid-lowering effects. Little work has been conducted with regard to its preloading in developing countries. This study aimed to analyze the effects of statin preloading in patients undergoing PCI in terms of reduction in major adverse cardiovascular events (MACE).

Methodology. This randomized controlled study was conducted at the Punjab Institute of Cardiology, Lahore for 6 months. A total of 186 patients undergoing elective PCI were included through non-probability consecutive sampling. Informed consent and demographic information were obtained. Two groups were formed, that is, the experimental group (receiving 80 mg atorvastatin prior to PCI) and the control group (not receiving atorvastatin before PCI). All patients were followed up at the intervals of 24 hours, 48 hours, and 1 month. MACE was calculated and data was analyzed in SPSS 26.0.

Results. The current study showed that the average age of participants was 55.10 ± 8.69 (age range 32-71 years). A total of 155 (83.33%) male participants and 31 (16.67%) female participants were enrolled for the study. Among the participants, there were 115 (61.8%) patients with diabetes mellitus, 102 (54.8%) with hypertension, 76 (40.9%) with dyslipidemia, and 91(48.9%) had a history of IHD. There were 10 patients who had major cardiovascular events. So, MACE came out to be 5.4%. Comparing both the groups, there were 2/93 (2.1%) patients in the experimental group who had MACE, whereas 8/93 (8.6%) patients had MACE in the control group. This difference was not statistically significant (p-value = 0.1).

Conclusion. Atorvastatin preloading before PCI reduces MACE by improving the perfusion of the myocardium.

Keywords: atorvastatin, major adverse cardiovascular events (MACE), percutaneous coronary intervention (PCI), preloading

Highlights

- Atorvastatin has the potential to decrease certain cardiovascular events during and after PCI due to its pharmacodynamics.

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- Although there was a difference in MACE between the two groups, still 80mg preloading of atorvastatin before PCI did not cause a significant reduction in MACE (*p*-value 0.1).
- The difference in the distribution of various risk factors and components of MACE (stroke, arrhythmia, myocardial infarction, stent thrombosis, and death) was not statistically significant either.

1. INTRODUCTION

Coronary artery disease (CAD) is the term used to describe a state of compromise in myocardial perfusion. It usually presents as angina or myocardial infarction (MI) [1]. The most common risk factors are hypertension, diabetes, obesity, atherosclerosis, and smoking [2]. It often leads to reduced exercise tolerance and congestive cardiac failure. During acute MI, it can cause the patient to land in cardiogenic shock and may also cause the rupture of the free wall or interventricular septum, acute mitral regurgitation, pericarditis, tamponade, and arrhythmias [3].

Coronary artery disease is a major public health problem across the globe. Universally, it is one of the leading causes of death in adult human population [4]. Moreover, its incidence in Pakistan is still on the rise [5].

Percutaneous coronary intervention (PCI) has become a common procedure for myocardial revascularization for the treatment of CAD. Although PCI reestablishes myocardial blood flow but it can damage the heart, resulting in various cardiovascular events. These may include, peri- and post-procedural MI and arrhythmias, acute kidney injury, bleeding from access site, stent thrombosis, and death [6, 7].

Statin drugs (including atorvastatin) are recommended as the first line lipid lowering agents and have a role in managing CAD [8]. There is substantial evidence available from previous studies that statins have beneficial pleiotropic cardiovascular effects as well [9]. A recent large scale trial on the preloading of atorvastatin before PCI showed its significance in reducing PCI-induced myocardial injury [10]. A randomized, double blind, placebo control trial was conducted by Otavio Berwanger *et al* regarding the efficacy of different doses of statins preloading in the reduction of post-PCI adverse events in 2018. This trial negated the findings of the previous trial since statins were proved to cause a non-significant reduction in MACE, with two early high doses of atorvastatin [11].

An earlier extensive review of randomized trials for the preloading dose of different statins before PCI was carried out by Lampropooulos et al in 2017 [12]. The effect was separately studied for different conditions. It showed a beneficial effect of the loading dose (80mg) of atorvastatin in the patients of stable angina [12].

Although there is some evidence available about the favorable outcomes of pretreatment with high dose statins in patients undergoing PCI, the evidence is still conflicting due to the limited and controversial data, mainly from Europe. Previous studies differed in preloading dose, timing of preloading, and outcomes. The evidence is especially lacking in South Asia. Moreover, no study from Pakistan has previously described any encouraging results of atorvastatin pretreatment in such patients. Statins are metabolized mainly by CYP 450 isoenzymes, whose activity

differs in Caucasian and Asian individuals. So, conflicting evidences with regard to statin preloading before PCI at different dosages and timings, differences in the quantified responses to statin based on ethnicity (due to the difference in CYP 450 activity), and the lack of literature are the main reasons of this study. Therefore, it is hypothesized that a high dose of atorvastatin preloading in patients having PCI would significantly reduce MACE. The results would be useful for the patients, trainees, and practitioners alike.

2. METHODOLOGY

The study aimed to compare the effects of atorvastatin preloading in patients undergoing PCI in terms of reduction in MACE. For this purpose, a randomized controlled trial was conducted at the Punjab Institute of Cardiology (PIC), Lahore for a duration of 6 months after getting permission from the ethical review board of the institution. A sample size of 186 was calculated (93 in each group) with an expected incidence of MACE on the 30th day at 5% in the intervention group (high statin group) and 18% in the control group in the patients of stable angina, prior to PCI [12]. All the patients of both gender in the age range of 25 to 80 years (who were compliant to medication and undergoing elective PCI) were included in the study. The patients who were either not compliant to medications or were not willing to take part in the study were excluded. Similarly, the patients with a history of myopathy, cerebrovascular accident or transient ischemic attack, chronic liver or kidney disease, and previous PCI and coronary artery bypass grafting were also excluded from the study.

A total of 186 patients from the Coronary Care Unit, Department of Cardiology, PIC were selected. Informed consent was taken from all of them. Information regarding demographic variables such as age and gender and risk factors such as a history of diabetes, hypertension, dyslipidemia, ischemic heart disease (IHD), and smoking was recorded. There were two groups of patients. Randomization was made using the lottery method with the help of sealed envelopes. The patients included in Group 1 (experimental /atorvastatin group) received 80 mg atorvastatin two hours before PCI, while the patients in Group 2 (control group) did not receive any statin. All patients received a maintenance dose of 40 mg atorvastatin for 30 days after the procedure. The patients were observed in CCU for 48 hours. Afterwards, they were followed up in OPD at 1 month interval. Post PCI complications such as acute kidney injury, peri-procedural MI, arrhythmias, stroke, and death were noted in both groups at the intervals of 24 hours, 48 hours, and 30 days. MACE was defined as the occurrence of any above mentioned post PCI complications excluding acute kidney injury.

Acute kidney injury was defined as a rise in serum creatinine of > 0.5 mg from baseline in 12 hrs or the doubling of serum creatinine in 48 hours. Whereas, peri-procedural MI was defined as per the criteria of American Heart Association [10]. Arrhythmias included atrial fibrillation, ventricular tachycardia, ventricular fibrillation, and AV blocks. Stent thrombosis was diagnosed with symptoms and ECG changes suggestive of an acute coronary syndrome and angiographic confirmation. MACE was assessed at the intervals of 24 hours, 48 hours, and 30 days after PCI.

All the collected data was entered into and analyzed by SPSS (version 26). Mean $\pm$ SD was calculated for quantitative

variables such as age and blood pressure. Frequency and percentages were calculated for qualitative variables including gender, history of diabetes, smoking, patients receiving statin and those not receiving statin before PCI, acute kidney injury, MI, stroke, arrhythmias, and death. Data was stratified for age, sex, patients receiving statin and not receiving statin, diabetes, hypertension, and smoking. Chi-square was applied to compare MACE in both groups. A *p*-value less than 0.05 was considered significant.

3. RESULTS

The findings of the current study showed that the average age of the participants was 55.10 ± 8.69 (age range 32-71 years). The study cohort comprised 155 (83.33%) male patients and 31 (16.67%) female patients.

There were 115 (61.8%) patients with diabetic mellitus (DM), while the number of smoker patients was 100 (53.8%). Similarly, the number of patients with a history of hypertension was 102 (54.8%) and with IHD was 91(48.9%). Whereas, there were 76 (40.9%) patients with a history of dyslipidemia and 10 patients with major cardiovascular events. So, MACE came out to be 5.4%. Descriptive statistics of all these variables are given below in Table 1.

Table 1. Descriptive Statistics with Respect to Risk Stratification in Both Groups

Variables	Risk Stratification	
	Yes	No
History of Diabetes Mellitus	115 (61.8%)	71 (38.2%)
History of Smoking	100 (53.8%)	86 (46.2%)
History of Hypertension	102 (54.8%)	84 (45.2%)
Family History of IHD	91 (48.9%)	96 (51.6%)
History of Dyslipidemia	76 (40.9%)	110 (59.1%)
MACE	10 (5.4%)	176 (94.6%)

Note. MACE: Major Adverse Cardiovascular Events; IHD: Ischemic Heart Disease

In comparison to both the groups, there were 2/93 (2.1%) patients in atorvastatin group who had MACE, whereas 8/93 (8.6%) patients had MACE in control group. Hence, there was a difference in both groups but it was not statistically significant (*p*-value = 0.1). There were 77/93 (82.8%) male patients and 16/93 (17.2%) female patients in atorvastatin group, whereas there were 78/93 (82.9%) male and 15/93 (16.1%) female patients in control group. The mean age in Group 1 (atorvastatin group) was 54.33± 8.81, while the mean age in Group 2 (control group) was 56.28± 8.50. There were 46 (24.73%) hypertensive patients in atorvastatin and 38 (20.43%) in control group. Further, there were 61 (32.80%) patients who had diabetes in atorvastatin group and 54 (29.03%) such patients were found in control group. Moreover, there were 53 (28.49%) smokers and 37 (19.89%) non-smokers in atorvastatin group, whereas 47 (25.27%) smokers and 49 (26.34%) non-smokers were found in control group. The results showed that there was no statistically significant difference between both research groups with respect to various risk factors such as DM, smoking, hypertension, history of IHD, and dyslipidemia with *p*-value > 0.05. The distribution of these risk factors in both the

groups and their association is explained in the table below.

Table 2. Descriptive Statistics with Respect to Risk Stratification in Both Groups

Variables		Study Groups		p-value
		Group 1 (Atorvastatin Group)	Group 2 (Control Group)	
Diabetes Mellitus	Yes	61 (67.8%)	54 (56.2%)	0.071
	No	29 (32.2%)	42 (43.8%)	
Smoking	Yes	53 (58.9%)	47 (49.0%)	0.113
	No	37 (41,1%)	49 (51.0%)	
Hypertension	Yes	46 (51.1%)	38 (39.6%)	0.76
	No	44 (48.9%)	58 (60.4%)	
Previous History of IHD	Yes	9 (10.0%)	6 (6.2%)	0.252
	No	81 (90.0%)	90 (93.8%)	
History of Dyslipidemia	Yes	2 (2.2%)	2 (2.1%)	0.665
	No	88 (97.8%)	97 (97.9%)	
MACE	Yes	2 (2.1%)	8 (8.6%)	0.1
	No	91 (97.9%)	85 (91.4%)	

The primary end point was MACE that was found to be 5.4%, overall. The events were not evenly distributed. It was found that 5 (2.7%) patients had stroke and another 5 (2.7%) had arrhythmias. There were 2 (1.1%) patients who developed MI and 1 (0.5%) patient had stent thrombosis. Only 1 patient expired during the study. The relative distribution of all these events in both the groups, their timings, and their association with the study group is given in the table below.

Table 3. Distribution and Association of Stratified Variables in Both Groups at Different Times

Variables	Assessment Time	Atorvastatin Group		Control Group		*p*-value
		Yes	No	Yes	No	
Stroke	At 24 hours	1 (1.1%)	92 (98.9%)	3 (3.22%)	90 (96.77%)	0.491
	At 48 Hours	0 (0.0%)	93 (100.0%)	1 (1.08%)	92 (98.92%)	0.361
	At 30 Days	0 (0.0%)	93 (100.0%)	0 (0.0%)	93 (100.0%)	0.414
Arrthymia	At 24 hours	1 (1.1%)	92 (98.9%)	3 (3.22%)	90 (96.77%)	0.491
	At 48 Hours	0 (0.0%)	93 (100.0%)	1 (1.08%)	92 (98.92%)	0.361
	At 30 Days	0 (0.0%)	93 (100.0%)	0 (0.0%)	93 (100.0%)	0.414
Myocardial Infarction	At 24 hours	0 (0.0%)	93 (100.0%)	1 (1.1%)	92 (98.9%)	0.679
	At 48 Hours	0 (0.0%)	93 (100.0%)	1 (1.08%)	92 (98.92%)	0.881
	At 30 Days	0 (0.0%)	93 (100.0%)	0 (0.0%)	93 (100.0%)	0.517
Stent Thrombosis	At 24 hours	0 (0.0%)	93 (100.0%)	0 (0.0%)	93 (100.0%)	0.001
	At 48 Hours	0 (0.0%)	93 (100.0%)	0 (0.0%)	93 (100.0%)	0.021
	At 30 Days	0 (0.0%)	93 (100.0%)	1 (1.08%)	92 (98.92%)	0.414
Death	At 24 hours	0 (0.0%)	93 (100.0%)	0 (0.0%)	93 (100.0%)	0.013
	At 48 Hours	0 (0.0%)	93 (100.0%)	0 (0.0%)	93 (100.0%)	0.034
	At 30 Days	0 (0.0%)	93 (100.0%)	1 (1.1%)	92 (98.9%)	0.784

No patient had acute kidney injury. The mean of serum creatinine in atorvastatin group was 1.79 ± 1.58 (mg/dl), while for control group it was 1.28 ± 2.06 (mg/dl) with a significant *p*-value = 0.004. The mean of CKMB in atorvastatin group was 13.26 ± 4.81U/l, while for control group it was 0.13.89 ± 6.27 u/l with an insignificant *p*-value = 0.224. Comparing creatinine levels at different times, there was no statistically significant difference found in mean creatinine level between atorvastatin and control groups, with *p*-value < 0.05 at 24 and 48 hours. However, at the 30th day, there was a significant difference found in mean creatinine level with *p*-value > 0.05.

Table 4. Comparison of Creatinine Levels at the Intervals of 24 Hours, 48 Hours, and 30 Days between Both Research Groups

Assessment Time	Group 1 (Atorvastatin Group)	Group 2 (Control Group)	*p*-value
	Mean ± S.D	Mean ± S.D	
At 24 hours	1.38± 3.63	1.18 ± 0.28	0.018
At 48 Hours	3.46 ± 10.76	1.10± 0.22	0.072
At 30 Days	3.12 ± 7.74	1.44± 1.66	0.005

4. DISCUSSION

The findings of the current study showed that the average age of participants was 55.10 ± 8.69 (age range 32-71 years). The mean age in Group 1 (atorvastatin group) was 54.33± 8.81, while in Group 2 (control group) was 56.28± 8.50. This difference was statistically insignificant, with a p-value > 0.960. There were 155 (83.33%) male patients and 31 (16.67%) female patients enrolled in the current study.

In the retrospective cohort study conducted by Alkhouli et al. [13] a total of 8.6 million patients underwent PCI, out of the 10.2 million enrolled patients. The mean age of the patients was 66.0 ±10.8 years, while 66.2% male as compared with 33.8 % female patients underwent PCI.[13] Another study conducted by Berwanger et. al (2018) enrolled 4191 patients with the mean age 61.8±11.5 years. There were 3106 (74.1%) male patients as compared with 1085 (25.9%) female patients [11].

The current study showed that the mean of serum creatinine in atorvastatin group was 1.79 ± 1.58 (mg/dl), while in control group it was 1.28 ± 2.06 (mg/dl) with a significant *p*-value = 0.004. The mean of CKMB in atorvastatin group was 13.26 ± 4.81u/l and it was 0.13.89 ± 6.27 u/l in control group with an insignificant *p*-value = 0.224. However, no acute kidney injury was reported. Zhao *et al* discovered that statins might dramatically improve lipid profiles; however, their role in improving the renal function in the patients of chronic kidney disease is still debated. They chose 33 RCTs with a total of 37,391 participants with chronic kidney disease. The findings revealed that statin treatment lowered urine albumin (*p* =.007) and protein (*p* =.002) levels. However, there were no significant differences in changes in the estimated glomerular filtration rate (*p* =.075) or serum creatinine level between the statin and control group. This established the renal safety of the drug [14].

MACE was not significantly different in both the groups (*p*-value > 0.05). The findings of the current study regarding

stroke and arrhythmia showed that there was no statistically significant difference found at the intervals of 24 hours, 48 hours, and 30 days with p-value > 0.05. Pan et al. [15] illustrated the role of a high dose of statin before PCI and found convincing results. There was a significant reduction in MACE, final thrombolysis in myocardial infarction (TIMI) flow grade, and myocardial injury during the procedure. In their meta-analysis, they considered 14 studies with a total of 3368 participants. MACE was reduced by 58% (p = 0.00001) after high-dose rosuvastatin preloading before PCI. The benefits for MACE were significant for both stable angina patients (p = 0.02) and ACS patients (p < 0.0001) and for both statin naïve patients (p < 0.0001) and previous statin therapy patients (p = 0.01) [15]. Similar results were also illustrated in another recent meta-analysis for atorvastatin [16]. The negative results of the current study might be attributed to small sample size and variable response to the drug in the selected population.

In this study, no death occurred in both atorvastatin and control group at 24 and 48 hours, but death did occur after 30 days. Research conducted by Elserafy et al. [17][17] found no statistical significance when comparing the two groups regarding in-hospital mortality from all causes and stroke following primary PCI [17]. This is in agreement with the results of the SECURE-PCI trial [11]. Another meta-analysis conducted in recent past encompassing all the cases of ACS showed a 20% reduction in MACE with atorvastatin. MACE reduction was statistically significant only in cases of ST segment elevation MI [18]. A non-significant decrease (p > 0.05) in MACE was also reported by Borovac *et al* in an analysis of 11 trials including more than 6000 patients [19].

Regarding MI at the intervals of 24 hours, 48 hours, and 30 days, there were insignificant differences found in atorvastatin group and control group with p-values > 0.05. The results are in agreement with those of a recent trial that showed a potential reduction in peri-procedural MI with atorvastatin loading dose [20].

A randomized, double-blind, control trial was conducted by Berwanger et al. [11] regarding the efficacy of statins in the reduction of post-PCI adverse events in 2018. In this study, 4191 patients were enrolled, out of which 2087 patients received two loading doses of atorvastatin 80 mg before and 24 hours after a planned early invasive approach. Whereas, 2104 received placebo prior to PCI (control group). The results of this trial among patients who underwent PCI indicated that routine administration of the two early doses of high-dose atorvastatin showed a non-significant reduction in MACE and non-PCI-related MI. The incidence of MI was 3.6% in statin group vs 5.2% in placebo group, while the incidence of MACE was 6.2% in statin group vs 7.1% in placebo group. This advantage was independent of the timing of statin administration [11].

Another randomized trial regarding the preloading dose of different statins before PCI was conducted by Lampropooulos et al in 2017 [12]. It showed a beneficial effect of the loading dose (80mg) of atorvastatin in the patients of stable angina. The study found that the high dose of atorvastatin not only reduced MACE but also significantly lowered MI incidence in such patients (p-value = 0.012) [12].

4.1. Limitations

There were certain limitations of the current study. This was a single center study with a limited sample size. The

outcome was not categorized for different disease presentations such as STEMI, NSTEMI, and unstable angina. The structural abnormality evident on echocardiography after the ischemic event was also not kept in consideration. The authors did a follow-up for a short duration. Statins are known to cause liver damage and muscle pain or soreness. They rarely cause rhabdomyolysis [21]. The tolerance and side effects of atorvastatin were not studied in the current study, with the follow up of the liver function test and muscle biopsy to look for myositis. A multi-center study with a larger population and a longer follow up to address these limitations is recommended for the future.

4.2. Conclusion

Preloading with a high dose of atorvastatin before PCI shows potential improvement in blood flow to myocardium and reduces MACE. So, the preloading dose of atorvastatin is recommended and a large multicenter trial is suggested to produce stronger evidence in literature to improve patient outcome.

CONFLICT OF INTEREST

The authors of the manuscript have no financial or non-financial conflict of interest in the subject matter or materials discussed in this manuscript.

DATA AVAILABILITY STATEMENT

The data associated with this study will be provided by the corresponding author upon request.

FUNDING DETAILS

No funding has been received for this research.

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