The Journal of Cardiovascular Diseases
J Cardiovasc Dis 2023;19(3):95 - 102

ORIGINAL ARTICLE
DOI: 10.55958/jcvd.v18i4.129

COMPARISON OF CLINICAL OUTCOME OF 20MG AND 40MG ROSUVASTATIN IN PATIENTS WITH ST ELEVATION ACUTE MYOCARDIAL INFARCTION (STEMI) AFTER PERCUTANEOUS CORONARY INTERVENTION (PCI) OVER 2 MONTHS

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Date of Submission: 04-01-2023; Date of Acceptance: 16-01-2023; Date of Publication: 15-02-2024

ABSTRACT:

BACKGROUND: *Diminished or total stoppage of blood circulation to a part of the myocardium leads to myocardial infarction (MI), frequently called "heart attack." MI is by and large associated with coronary artery disease. Atherosclerosis is the predominant cause of CAD. Atherosclerosis is a result of dyslipidemia. Statin is a lipid-lowering medication that also has anti-inflammatory properties, lowers oxidative stress, inhibits thrombogenic responses, stabilizes plaque, and improves endothelial function, resulting in enhanced myocardial perfusion. This research was designed because medical evidence on the advantages of 20mg rosuvastatin versus 40mg rosuvastatin for lowering peri-procedural myocardial injury and post PCI MACE in patients suffering from STEMI is limited in the Pakistani population.*

AIMS & OBJECTIVE: *The goal of this research work was to compare the clinical outcomes of using 20mg and 40mg rosuvastatin following percutaneous coronary intervention (PCI) in individuals suffering from STEMI over 2 months.*

MATERIAL & METHODS: *For six months, a RCT was conducted in the Cardiology department of Mayo Hospital, Lahore. Sixty-six patients were included after fulfilling the inclusion and exclusion criteria. Individuals enrolled in this trial were randomized to 2 groups: group A, in which patients were given 20 mg Rosuvastatin and group B, in which patients were given 40mg Rosuvastatin. All patients received PCI by experienced interventional cardiologists. Clopidogrel was prescribed for a year after the intervention, and aspirin was prescribed for lifelong. After 24 hours, 1 week, 6 weeks, and 2 months, patients in both groups were re-evaluated clinically.*

RESULTS: *The patient's mean age was 48.42±9.127 years, with 51 (77.27%) of them being male and 25 (37.86%) of them being diabetic. In terms of quantitative TnI, CKMB, ALT, HDL, LDL, TG, TC, and HbA1c, there was no significant difference among the two groups. Tolerability for both 20mg and 40 mg rosuvastatin was 100 percent at the end of the second month. In both groups, no MACE was found.*

CONCLUSION: *This research concluded that 40 mg rosuvastatin is just as safe and well tolerated as 20 mg rosuvastatin. After two months of PCI in individuals suffering from STEMI, both intensities are equally effective in terms of clinical outcome.*

KEY WORDS: *Myocardial Infarction, Rosuvastatin, Percutaneous Coronary Intervention, lipid profile, ST segment elevation myocardial infarction*

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Author's Contribution: IA: Literature search. BM: Literature review, concept, manuscript writing and drafting. WA: Literature review, manuscript writing and drafting. TAB: Literature review.FYP: Literature review. AS: Data analysis.

INTRODUCTION:

According to the 2017 Global Burden of Disease Study, cardiovascular illnesses account for 31.8 percent of all mortalities globally, with ischemic heart disease contributing to half of those deaths. Among ischemic heart disease, AMI (acute myocardial infarction) is the main reason of morbidity and mortality. Its mortality rate is decreasing internationally, although it is still extremely high in low- and middle-income nations. It is the leading cause of premature deaths globally.[1, 2] Atherosclerosis is an inflammatory condition of the arteries linked with depositions of lipids in addition to changes in metabolism owing to various risk factors, and is the primary pathological condition that contributes to Ischaemic heart disease.[3] According to 10th atlas of international diabetes federation 26.7% of Pakistan's population is known diabetic and 14.4% are pre-diabetics making uncontrolled diabetes an exigent pro-atherogenic condition.[4] In order to reduce the likelihood of MI, it is crucial to alter the underlying pathophysiology of plaque rupture leading to thrombosis in patients presenting with CAD.[5] Because PCI has been shown to be quite more effective than thrombolysis, and as a result of medical research and technology advancements, many of these patients are being assessed and treated quite rapidly and invasively with cardiac catheterization and subsequent PCI, resulting in its widespread use as the preferred reperfusion strategy. The following are the three types of problems that might develop during PCI: (A) cardiac, (B) vascular access-site-related issues, and (C) other problems such as impairment of kidney function (also known as contrast-induced nephropathy (CIN)), cholesterol embolism and thrombocytopenia.[6] Procedure related Myocardial Injury / Infarctions are classified as type 4a MI when cardiac Troponin levels are elevated 5 times from baseline value or are above the 99th percentile URL, according to MI's fourth universal definition.[7,8] Acute coronary syndrome management does not end with revascularization, such as PCI or coronary artery bypass grafting; instead, secondary preventative interventions are an important part of patient treatment.[9] Lipid lowering is one of these measures, which has demonstrated cardiovascular benefit. According to American Heart Association (AHA) guidelines, individuals with ACS must be prescribed statin medication to attain a 50 percent reduction in LDL-C from baseline or a level below 70 milligram/deciliters or as low as possible. LDL-C levels under 55 milligram/deciliters are recommended by the ESC.[10] The statins are categorized as high, moderate, and low intensity on the basis of LDL-C reduction of greater than 50%, 30 to 49%, and less than 30%, respectively. When compared to moderate-intensity statin medication, high-intensity statins lowered major vascular events by 15% while having insignificant effect on coronary death rate. It lowers the risk of all-cause mortality in individuals with ventricular tachyarrhythmias.[11] Kim et al.[12] discovered that high intensity rosuvastatin uptake before primary PCI enhances microvascular myocardial perfusion, resulting in a reduced infarct size. According to a meta-analysis of fourteen studies, high intensity rosuvastatin given before PCI enhances microvascular myocardial perfusion, reduces ischemia-reperfusion injury[13], significantly lowers MACE, periprocedural myocardial damage, and infarction[14], and improves long-term clinical outcomes.[15] In a study done in India, 40 milligram rosuvastatin medication was shown to be well tolerated and safe in individuals with acute coronary syndrome.[16] In Asian patients and patients with STEMI, there is little clinical data on the beneficial effects of 40mg versus 20mg rosuvastatin for lowering peri-procedural myocardial damage and post PCI MACE. The primary objective of our study is to appraise the efficacy and safety of rosuvastatin in lowering adverse cardiovascular outcomes in patients with STEMI following admission in hospital for PCI (within 24 hrs. of the beginning of symptoms suggesting ischemia).

Objective

To compare the clinical outcomes of using 20mg and 40mg rosuvastatin following percutaneous coronary intervention (PCI) in individuals suffering from STEMI over 2 months.

MATERIALS AND METHODS:

This randomized controlled trial was conducted in the Cardiology Department of Mayo Hospital, Lahore within the time period of six months after synopsis approval. Patients were selected using probability simple random sampling. They were randomized to 20mg or 40mg rosuvastatin using computer generated random number table. A total

of 66 cases fulfilling the inclusion/exclusion criteria were enrolled from the Department of Cardiology Mayo Hospital, Lahore. All the patients with >18 years of age, diagnosed with STEMI, within 24 hours of ischemic symptoms onset were included in the study. Patients younger than 18 years of age, patients with NSTEMI, patients with >24hrs time passed since onset of ischemic symptoms, patients who had contraindications of coronary angiography or PCI, patients in whom study drug is contraindicated like pregnant and lactating women, liver disease such as acute hepatitis or liver cirrhosis (except for fatty liver) (ALT level >3x UNL), known allergy/intolerance to study drugs, known skeletal muscle disease were excluded from the study. Baseline clinical assessment, plasma CK-MB, quantitative TnI, ALT, HbA1c and an echocardiographic Doppler evaluation was performed. Patients were randomized to group-A (20mg Rosuvastatin) or group-B (40mg Rosuvastatin) using a computer-generated random number table. Aspirin (300 mg) and Clopidogrel (300 mg) were given before PCI. Group-A was assigned to 20mg Rosuvastatin once daily and continued for next 2 months. Group-B were assigned to 40mg Rosuvastatin once daily and continued for next2 months. All patients received PCI by experienced physicians using a standard technique of intervention. PCI is labeled as successful when there is less than 20 percent residual stenosis and TIMI III flow is achieved. After PCI, daily 75 mg Clopidogrel was prescribed for one year along with daily 150mg aspirin for life. Other guideline directed medical therapy was given as indicated. Patients from both groups were reevaluated clinically after 24hrs, 1 week 6 weeks and 2 months after PCI. All data was recorded by the researcher herself on the specified proforma. All data was fed and analyzed using SPSS version 26. Qualitative data like gender, diabetic & non diabetic, MACE was presented in the form of frequency (%). The quantitative data like age, height, weight, BMI, plasma levels of CK-MB, ALT, quantitative TnI and HbA1c was presented in the form of mean ± standard deviation. Comparison between 20mg Rosuvastatin and 40mg Rosuvastatin applies paired t test. p-value ≤ 0.05 was considered as significant.

RESULTS:

In this study a total of 66 patients participated. The mean age of the patients was 48.42±9.127 years. In our study 51(77.27%) patients were male and 15(22.73%) patients were females. In group A the mean BMI of the patients was 27.34±3.42 kg/m^2 and in group B the mean BMI of the patients was 26.84±2.78 kg/m^2. In our study 25 (37.86%) patients were diabetic, 28(42.42%) were non-diabetic and 13(19.70%) were pre-diabetic (Table 1).

25 U/L was the upper limit of normal reference value. At baseline the mean CKMB value in group A patients was 77.97±101.99 and in group B the mean CKMB value was 52.18±40.76 (p-value=0.182). At 24 hours the mean CKMB value in group A patients was 72.45±64.42 and in group B the mean CKMB value was 80.17±104.85 (p-value=0.728). At 1st week the mean CKMB value in group A patients was 29.85±42.79 and in group B the mean CKMB value was 21.36±10.08. Normal upper reference limit of Troponin I was 0.02 ng/mL. At baseline the mean quantitative TnI in group A patients was 3.13±6.41 and in group B the mean quantitative TnI value was 6.86±11.00 (p-value=0.097). After 24 hours, the mean quantitative TnI in group A patients was 13.22±12.66 and in group B the mean quantitative TnI value was 6.96±10.84 (p-value=0.035). In follow-up of at 1st week, in group A the mean quantitative TnI of the patients was 12.34±34.38 and in group B its mean value was 1.05±2.13 (p-value=0.069). Normal reference value of ALT was considered as up to 34 U/L. At baseline in group A the mean ALT of the patients was 34.09±37.53 and in group B the mean ALT was 29.24±15.02 (p-value=0.493). At 24 hours in group A the mean ALT of the patients was 40.97±32.69 and in group B the mean ALT was 30.03±15.08 (p-value=0.086). At 1st week in group A the mean ALT of the patients was 29.12±17.40 and in group B the mean ALT was 30.69±23.77 (p-value=0.760). At baseline in group A the mean HbA1c of the patients was 6.45±1.65% and in group B the mean HbA1c was 6.66±1.45% (p-value=0.591). At 6th week in group A the mean HbA1c of the patients was 6.46±1.68% and in group B the mean HbA1c was 6.57±1.56% (p-value=0.797). At baseline in group A the mean LDL of the patients was 86.81±28.21 mg/dl and in group B the mean LDL was 87.75±31.28 mg/dl (p-value=0.897). At 6th week in group A the mean LDL of the patients was 91.12±29.64 mg/dl and in group B the mean LDL was 77.66±30.67 (p-value=0.075). At baseline in group A the mean HDL of the patients was 34.73±10.03 mg/dl and in group B the mean HDL was 33.15±7.84 mg/dl (p-value=0.796). At

Table 1: Baseline characteristics		
Gender	Male	77.2% (n=51)
	Female	22.73% (n=15)
Mean BMI of Patients	Group A	27.34±3.42 kg/m^2
	Group B	26.84±2.78 kg/m^2
Diabetes	Diabetic (n=25)	37.86%
	Non-diabetic (n=28)	42.42%
	Pre-diabetic (n=13)	19.70%

Table 2: Comparison of BioChemical lab results at 24 hours and 1 week.				
		Group A (n=33)	**Group B (n=33)**	**p-value**
CKMB	Baseline	77.97 ± 101.99	52.18±40.76	0.182
	24 Hours	72.45±64.42	80.17±104.85	0.728
	1st week	29.85±42.79	21.36±10.08	0.272
	p-value (within group)	0.012	0.0002	
Quantitative TnI	Baseline	3.13±6.41	6.86±11.00	0.097
	24Hours	13.22±12.66	6.96±10.84	0.035
	1st week	12.34±34.38	1.05±2.13	0.069
	p-value (within group)	0.275	0.298	
ALT	Baseline	34.09±37.53	29.24±15.02	0.493
	24 Hours	40.97±32.69	30.03±15.08	0.086
	1st week	29.12±17.40	30.69±23.77	0.760
	p-value (within group)	0.386	0.780	
HbA1c	Baseline	6.45±1.65	6.66±1.45	0.591
	6th week	6.46±1.68	6.57±1.56	0.797
	p-value (within group)	0.744	0.375	
LDL	Baseline	86.81±28.21	87.75±31.28	0.897
	6th week	91.12±29.64	77.66±30.67	0.075
	p-value (within group)	0.289	0.014	
HDL	Baseline	34.73±10.03	33.15±7.84	0.796
	6th week	39.21±36.86	30.73±12.05	0.213
	p-value (within group)	0.487	0.160	
Triglycerides (mg/dl)	Baseline	182.61±125.63	283.54±381.25	0.153
	6th week	312.36±406.65	222.33±235.08	0.275
	p-value (within group)	0.104	0.432	
Total cholesterol (mg/dl)	Baseline	173.67±42.58	179.51±56.26	0.636
	6th week	177.06±46.27	150.91±58.15	0.047
	p-value (within group)	0.657	0.003	

6th week in group A the mean HDL of the patients was 39.21±36.86 mg/dl and in group B the mean HDL was 30.73±12.05 mg/dl (p-value=0.213). At baseline in group A the mean TGL of the patients was 182.61±125.63 mg/dl and in group B the mean TGL was 283.54±381.25 mg/dl (p-value=0.153). At 6th week in group A the mean TGL of the patients was 312.36±406.65 mg/dl and in group B the mean was 222.33±235.08 (p-value=0.275). At baseline in group A the mean total cholesterol of the patients was 173.67±42.58 mg/dl and in group B the mean total cholesterol

Table-3: MACE at 6 weeks and 2 months.

	Study Groups		Total	p-value
	Group A	Group B		
Arrhythmia	0	0	0	>0.999
Cardiac death	0	0	0	
Rehospitalization	0	0	0	
Recurrence of angina	0	0	0	
Surgery or PCI	0	0	0	
Stroke	0	0	0	
Tolerability	100%	100%	100%	

was 179.51±56.26 mg/dl (p-value=0.636). At 6th week in group A the mean total cholesterol of the patients was 177.06±46.27 mg/dl and in group B the mean total cholesterol was 150.91±58.15 mg/dl (p-value=0.047) (Table 2).

After 6 weeks, arrhythmia was absent in all patients in both groups (p>0.999), after 2 months, arrhythmia was absent in all patients in both groups (p>0.999). After 6 weeks, cardiac death was absent in all patients in both groups (p>0.999) . After 2 months, cardiac death was absent in all patients in both groups (p>0.999). After 6 weeks, re-hospitalization was not done in all patients in both groups (p>0.999). After 2 months, re-hospitalization was not done in all patients in both groups (p>0.999). After 6 weeks, recurrence of angina was absent in all patients in both groups (p>0.999). After 2 months, recurrence of angina was absent in all patients in both groups (p>0.999). After 6 weeks, surgery or PCI was not done in all patients in both groups (p>0.999). After 2 months, surgery or PCI was not done in all patients in both groups (p>0.999). After 6 weeks, stroke was absent in all patients in both groups (p>0.999). After 2 months, stroke was absent in all patients in both groups (p>0.999). After 6 weeks, tolerability was noted in all patients in both groups (p>0.999). After 2 months, tolerability was noted in all patients in both groups (p>0.999) (Table 3).

DISCUSSION:

Percutaneous coronary intervention is the prevailing reperfusion strategy in patients with coronary artery disease. Although PCI is a safer procedure, severe complications do happen like peri-procedural myocardial infarction (PMI). PMI is assessed by elevation in cardiac markers. It happens in 5% to 40% of patients, relying on the defining criteria being applied, antithrombotic therapy persuasion, and clinical/angiographic risk profile of the patient. It negatively impacts clinical outcome after intervention.[17,18] In this study no significant difference was found in the outcome of patients between high (20mg) and very high (40mg) intensity groups of Rosuvastatin. However good control was observed in the very high intensity Rosuvastatin group. 40mg Rosuvastatin was as well tolerated as 20mg. Both of them are safe and no new onset of diabetes or unmasking of diabetes observed. Veselka et al.[19] demonstrated 17% and 16% incidence of periprocedural myocardial infarction in the atorvastatin group and the control group, respectively (p = 0.85). It showed that pre-procedural administration of atorvastatin did not reduce the incidence of PMI in patients with stable angina undergoing elective PCI. Veselka et al.[20], who demonstrated no effect of high-dose rosuvastatin therapy on the incidence of PMI in patients with stable angina.

According to the ARMYDA and ARMYDA-ACS trials, a short-term pretreatment with atorvastatin prior to PCI in ACS patients who are statin-naïve, has a significant reduction of PMI.[21] In the ARMYDA-RECAPTURE trial, [22] patients who were before now taking statin therapy were reloaded with a high intensity atorvastatin before PCI. It showed better periprocedural outcome in patients who received reloading dose. Ziliang Ye et al.[23] showed in their study that the loading dose (20mg/day) of rosuvastatin was more advantageous than conventional dose (10mg/day) given to ACS patients and is appropriate for clinical practice. A recent study reported that mean CK-MB after 24 hours of PCI in 20mg rosuvastatin was 59.77± 17.31 and in 40mg rosuvastatin was 39.54± 13.25. The mean ALT was 28.54± 6.98 with 20mg rosuvastatin and 24.15± 10.25 with 40mg rosuvastatin. The mean TnI24hrs Post PCI in

20mg rosuvastatin was 1.85± 0.59 and in 40mg rosuvastatin was 1.16±0.72. Further they reported that the mean Cumulative MACE was 15 (46.9) in 20mg rosuvastatin group and 3(8.8) in 40mg rosuvastatin group, p-value < 0.05.17. Yun KH12 performed a follow-up after one year in a trial done in 2011. 445 ACS cases who go through PCI were entered in this study and randomized to either rosuvastatin group (n = 225) or control group (n = 220). Rosuvastatin group received a 40mg rosuvastatin loading dose before PCI in contrast to the control group in which there was no statin used before intervention. Cardiac mortality, non-lethal MI or stroke and any ischemia-driven revascularization after 12 months were the endpoints of this study. This study showed that major adverse cardiac events occurred in 20.5% and 9.8% of patients enrolled in the control group and the rosuvastatin group, respectively (p = 0.002). The mortality rate and non-lethal myocardial infarction were significantly higher in the control group (p = 0.021). Finally, Yun demonstrated that loading with high intensity rosuvastatin prior to PCI can significantly ameliorate one-year clinical outcomes in acute coronary syndrome patients. The loading dose of rosuvastatin was proved superior to the conventional dose by many studies conducted in the patients with ACS.[24,25] Cay performed a trial in which 299 cases were enrolled.[26] 153 individuals were entered into Rosuvastatin group and other 146 individuals participated into no-treatment group. Rosuvastatin treatment group received a loading dose of 40 milligram rosuvastatin 24 hours before PCI. CKMB and TnI levels were measured before PCI and at 12 hours following PCI. Rosuvastatin group has significantly lower elevation in CKMB and cTnI as compared to the control group (0.7% vs. 11.0% CK-MB elevation, p<0.001 and 10.5% vs. 39.0% cTnI elevation, p<0.001, respectively). It is inferred from this study that loading with high intensity rosuvastatin (40 mg/day) effectively lowers the PMI incidence. Chetan P. Shah et al.[27] documented that a 40 milligram rosuvastatin, started early and continued for 12 weeks, was well tolerated and efficacious in reducing LDL cholesterol. Yilong Pan et al.14 concluded in their study that loading with high dose rosuvastatin can significantly boost myocardial perfusion and reduce major adverse cardiovascular events including peri-procedural myocardial injury in patients receiving PCI. Rosuvastatin preloading has significant cardioprotective benefits in both stable angina and ACS patients and also in statin naïve patients and individuals who were already taking statin therapy. The cardioprotective benefits of Rosuvastatin preloading especially in acute coronary syndrome and statin naïve patients were observed in the follow-up period. Observed benefits include a reduction in spontaneous MI and TVR. As contrary results observed in previously published studies as compared to our study results, this may be due to the small sample size used in this study. 5 years Number needed to treat with statin therapy for secondary prevention of mortality and non-fatal MI is 1 in 83 and 1 in 39, respectively.[28] In JUPITER trial Rosuvastatin was used for primary prevention of MI, showing a 5 years NNT of 1 in 32 and 2 years NNT of 1 in 98.29 Hence, we need a larger sample size to observe significant difference. The second reason may be that many of the previous studies followed the patients for a long time but in our study follow-up of patients was not that much longer.

CONCLUSION:

This research concluded that 40 mg rosuvastatin is just as safe and well tolerated as 20 mg rosuvastatin. After two months of PCI in individuals suffering from STEMI, both intensities are equally effective in terms of clinical outcome. However, the data suggests that 40 mg is superior to 20mg but our study was not statistically powered and long enough to show a significant difference.

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