Impact of Routine Early High-Dose Rosuvastatin Preloading on The Outcomes of Primary PCI in Anterior STEMI Patients Presenting within 12 Hours of Symptoms: A Randomized Controlled Trial

Ihab Yassin[1], Ahmed Gewifal[1], George Ghaly[2]

Lecturer of cardiovascular medicine in the National heart institute[1], Lecturer of cardiovascular medicine in the Sahel teaching hospital[2]

***Corresponding** Author**:** Ihab Yassin**,** Email: ihappy71@hotmail.com
Address: 8 Al Maqdesi Al Qabari street,7th district, Nasr city, Cairo, Egypt
Phone Number:00201022391337

Abstract

Objectives: There are no enough data regarding the clinical outcomes, including mortality and morbidity, after the administration of a high preloading dose of statins before primary percutaneous coronary intervention (PPCI). Therefore, in this randomized control trial, we aimed to evaluate the impact of routine early high dose rosuvastatin preloading on the outcomes of PPCI in anterior ST-elevated myocardial infarction (STEMI) patients presenting within 12 hours of symptoms.

Methods: We conducted a randomized, controlled, trial that enrolled male, diabetic, patients who were admitted with anterior STEMI and were eligible for PPCI. Eligible patients were allocated to 40 mg rosuvastatin or control group. The primary endpoint in our study was the measurement of major adverse cardiovascular and cerebrovascular events (MACCE) one-month after the procedure.

Results: A total of 40 patients were included during the study period and divided into equal ratio to study's groups. Concerning the post-procedural laboratory findings, the post-procedural serum creatinine was significantly lower in the rosuvastatin group than the control group (p =0.05). Notably, the rosuvastatin group had numerically lower Hs-CRP values than the control group (p =0.331). In evaluating MACCEs, the rosuvastatin

group had no reported cases of in-hospital or one-month MACCE, compared to two cases of MAACE during in-hospital stay (one death and one reinfarction) in the control group (p =0.14). Similarly, during our one-month follow-up, two more cases of MACCE were reported**,** including one stroke and one reinfarction, giving a total MACCE of four cases or 20% in the control group in comparison to 0% among the rosuvastatin Group. However, this numerical significance failed to translate into a significant statistical result with a *P*-value of 0.147.

Conclusion: There is a trend towards better clinical outcomes following a high loading dose of rosuvastatin in patients undergoing PPCI. However, this study failed to reach the level of statistical significance.

Keywords: Myocardial infarction; STEMI; Atorvastatin; Primary PCI;

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Introduction

In patients with ST-segment elevation myocardial infarction (STEMI), the main target is to restore the blood flow of the epicardial coronary artery and preserve the myocardial tissue perfusion, which can be achieved currently with the Primary percutaneous coronary intervention (PPCI) [1,2]. Although PPCI can reopen most infarction-related arteries in patients with STEMI, it is often difficult to achieve continuous restoration of epicardial blood flow and/or adequate myocardial perfusion [3,4].

In some cases, the PPCI can open the epicardial artery; however, there is no flow into the myocardium, which is known as the no-reflow phenomenon, predicting consequences and adverse remodeling of the left ventricle [5–7]. Therefore, effective adjuvant therapies that can enhance the myocardial tissue perfusion and epicardial blood flow are in great demand.

The advantages of statin for coronary artery diseases are well established in primary and secondary prevention. Earlier studies have shown statins to have many protective effects, including stabilization of atherosclerotic plaque, endothelial function improvements, and reduced oxidative stress, inflammation, and thrombogenic reaction, which have not been specifically associated with their influence on lipid metabolism [8–10]. These effects can help to preserve microvascular function during ischemia and after STEMI reperfusion [11]. In patients with elevated levels of serum C-reactive protein, a high-dose of preloading statins was more efficient, according to Naples II and the ARMIDA-RECAPTURE trials [12,13]. Therefore, high-dose statin loading therapy in ST-segment myocardial elevation (STEMI) patients can be more effective than in other clinical circumstances because STEMI is associated with extremely high inflammation [14]. Moreover, the current guidelines recommended administrating statins as early as possible in acute coronary syndrome patients, regardless of the baseline cholesterol levels [14,15]. The STATIN-STEMI trial showed that a high loading dose of atorvastatin enhanced the post-PPCI coronary flow and perfusion; however, their sample was too small to draw a definite conclusion [16]. Furthermore, there are no enough data regarding the clinical outcomes, including mortality and morbidity after the administration of a high preloading dose of statins before PPCI.

Therefore, in this randomized control trial, we aimed to evaluate the impact of routine early high dose rosuvastatin preloading on the outcomes of PPCI in anterior STEMI patients presenting within 12 hours of symptoms.

Material and Methods

The preset trials adhered to the standards of the Declaration of Helsinki and the guidelines of good clinical practice (GCP), we confirm that none of the study's procedures violated any of these standards or relevant regulatory laws, and all procedures started only after obtaining the proper ethical clearance from the responsible committee in the participated centers. All eligible patients were included after signing the written informed consents by themselves or first-degree relatives. We followed CONSORT statement during the preparation of this manuscript[17].

Study Design and Population

We conducted a randomized, controlled, trial that enrolled male, diabetic, patients who were admitted to the Emergency Departments of the National Heart Institute and Al-Sahel Teaching Hospital, Egypt. Patients were deemed eligible if they presented with the first attack of ischemic heart disease in the form of anterior STEMI and were eligible for primary PCI. We excluded patients with history of regular statin therapy, cardiogenic shock, significant hepatic or renal impairments, inflammatory or autoimmune diseases, and/or patients with advanced malignancy.

Randomization and Study's Interventions

Following initial screening and informed consent, eligible patients were randomly allocated, using a computer-generated sequence, to rosuvastatin or control groups. In the rosuvastatin group, patients received 40 mg rosuvastatin tablets before undergoing primary PCI and continued on a maintenance dose of 20 mg/day, in addition to the standard regimen. In the control group, patients received the standard regimen only.

Data Collection and PCI Procedure

Patients were subjected to history taking, full clinical examination, routine laboratory investigations, baseline 12-lead electrocardiogram ECG findings., echocardiography, and diagnostic coronary angiography. The primary PCI was performed according to local institutional guidelines. Before the procedure, all patients received a loading dose of 300mg aspirin, 600mg clopidogrel, 5000 I.U of intravenous unfractionated heparin; the heparin dose was administered during the procedure. All angiographic complications during PCI were noted and recorded.

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.

Follow-up and Study Endpoints

All patients were followed-up for one month after primary PCI(PPCI). The primary endpoint in our study was the measurement of major adverse cardiovascular and cerebrovascular events (MACCE), described as in-hospital all-cause death, AMI, or

ischemic stroke. Secondary outcomes involved contrast induced nephropathy,complete heart block, sudden cardiac arrest, and cardiogenic shock.

Analysis of Results

The conduction of data analysis was performed via SPSS software (SPSS Inc., Chicago, IL, USA) version 22 for Microsoft Windows. Appropriate descriptive measures were used to describe numerical and categorical variables according to the normality of the data. The hypothesis of a significant association between quantitative variables was tested by unpaired t-test or Mann-Whitney Rank Sum test per data normality. The Chi-square test was implemented to identify the level of significance for categorical variables. The statistical associations were considered significant at a p-value of <5%.

Results

A total of 40 patients were included during the study period and divided into equal ratio to receive 40 mg rosuvastatin or normal regimen alone. There were no statistically significant differences between the rosuvastatin and control groups as regards the age in (54.85±13.41 versus 56±8.28, respectively; p = 0.75), smoking (85% versus 95%, respectively; p =0.48), systolic blood pressure 123 ± 20.54 versus 122.5± 22.91mmHg, respectively; p =0.94), diastolic blood pressure (76.50± 12.15 versus 78.75± 13.56mmHg, respectively; p=0.58), and Killip Class (**Table 1**).

Table 1: Demographic Characteristics of the Included Patients

Variable	Rosuvastatin (n=20)	Control (n=20)	P-value
Age (yrs)	54.85±13.91	56 ±8.28	0.752
Smoker (%)	85%(17)	95%(19)	0.486
SBP (mmhg)	123.00±20.54	122.50±22.91	0.942
DBP (mmhg)	76.50±12.15	78.75±13.56	0.584
Killip Class (%)	Class I (100%)	Class I (100%)	

As shown in **Table 2**, both rosuvastatin and control groups had similar procedural characteristics including angiographic findings (p =0.2), use of aspiration device (p =0.3) use of GPI (p =0.2), TIMI flow (p =0.46), and myocardial blush grading (p =0.78).

Table 2: Procedural data

Variable		Rosuvastatin (n=20)	Control (n=20)	P-value
Angiographic findings:	Single vessel disease Multi vessel disease	65% (13) 35% (7)	80% (16) 20% (4)	0.288
Aspiration device:		25% (5)	40% (8)	0.311
GPI:		60% (12)	40% (8)	0.206
TIMI Flow:	Grade 2 Grade 3	30% (6) 70% (14)	20% (4) 80% (16)	0.465
Myocardial blush grading:	1 2 3	5% (1) 70% (14) 25% (5)	5% (1) 60% (12) 35% (7)	0.784

Concerning the post-procedural laboratory findings, the post-procedural serum creatinine was significantly lower in the rosuvastatin group than the control group (p =0.05). Notably, the rosuvastatin group had numerically lower Hs-CRP values than the control group (p =0.331). There were no significant differences between both groups regarding the leucocytic count (p =0.31). Half of the patients in the rosuvastatin group were found to have mitral regurgitation, compared to 65% of the patients in the control group. No statistical significance could be noted here as well. Both groups had comparable ejection fraction as well (46.75±10.427 versus 48±7.66%, respectively; p =0.66). Concerning diastolic dysfunction, 45% of rosuvastatin group patients had diastolic dysfunction of varying grades in contrast to 65% of control group patients (**Table 3**).

In evaluating MACCEs, the rosuvastatin group had no reported cases of in-hospital or one-month MACCE, compared to two cases of MAACE during in-hospital stay (one death and one reinfarction) in the control group (p =0.14). Similarly, during our one-month follow-up, two more cases of MACCE were reported**,** including one stroke and one reinfarction, giving a total MACCE of four cases (20%) in the control group in comparison to 0% among the rosuvastatin Group. However, this numerical significance failed to translate into a significant statistical result with a *P*-value of 0.147 (**Figure 1**).

Table 3: Comparison between the two studied groups regarding Laboratory results and Echocardiographic findings

Variable		Rosuvastatin (n=20)	Control (n=20)	P-value
WBC ($mm^{3)}$		9.635±3.721	10.830±3.578	0.307
HGB (g/dl)		13.60±1.754	13.03 ±1.539	0.282
PLT (mm^3)		228.80±67.018	253.90±59.137	0.217
ALT (U/L)		31.90±27.732	33.60±10.510	0.799
AST (U/L)		39.60±11.222	38.20±11.959	0.705
Creat (mg\dl)		0.920±0.285	1.080±0.2215	**0.055**
CK total IU\L		911.45±532.31	764.60±527.4	0.386
Urea (mg\dl)		35.45±12.103	33.55±18.43	0.702
Hs CRP	Pre	6.150±1.392	11.025±3.997	0.000
	Post	11.040±1.265	20.340±3.164	0.000
	% change	86.13±34.4	101.11±58.72	0.331
Echo Finding:%(n)	**MR**	50% (10)	65 (13)	0.377
	DD	45% (9)	65% (13)	0.204
	EF	46.75±10.427	48.00±7.66	0.668

Discussion

There are controversies regarding the clinical benefit of a high preloading dose of statins before PPCI. Therefore, we found it imperative to evaluate the impact of routine early high dose rosuvastatin preloading on the outcomes of PPCI in anterior STEMI patients presenting within 12 hours of symptoms in a well-designed, controlled, trial. Our results demonstrated that despite the numerical benefit of rosuvastatin preloading on the incidence of one-month MACCEs, the clinical benefit of rosuvastatin preloading did not

reach the level of statistical significance. On the other hand, the post-procedural serum creatinine was significantly lower in the rosuvastatin group than the control group; which highlights that rosuvastatin preloading before PPCI had renal protective effects and can help in preventing contrast-induced acute kidney injury (CI-AKI). There was a trend towards lower Hs-CRP following rosuvastatin preloading indicating an anti-inflammatory effect of rosuvastatin; however, the percentage change, in comparison to the control group, was not statistically significant.

Statin is a well-established protective therapy for primary and secondary coronary artery diseases, which exhibits anti-inflammatory, anti-oxidative stress, and anti-thrombogenic effects; besides, previous experiments demonstrated that statins significantly stabilized atherosclerotic plaque[8–10]. Owing to these beneficial effects – especially the anti-inflammatory-role-, recent studies have tried to identify whether statin can preserve microvascular function after STEMI reperfusion [11–13]. As previously stated, the high loading dose of atorvastatin was found to enhance the post-PPCI coronary flow and perfusion[16]. Nonetheless, whether the enhancing effect of rosuvastatin preloading has a significant impact on the post-PPCI clinical outcomes has not been elucidated yet. In this study, we found that the clinical benefit of rosuvastatin preloading did not reach the level of statistical significance and, thus, no conclusive evidence could be drawn here. Such findings are in line with a recent Egyptian experience by Elserafy et al.[18], in which the rosuvastatin preloading did not provide additional clinical benefit in patients with STEMI undergoing PPCI. Other clinical trials demonstrated no further benefit of rosuvastatin preloading on the clinical outcomes of STEMI patients undergoing PPCI[19,20]. Nonetheless, our findings contradict the results of the 2015 systematic review by Pan et

al.[21]; in this review, 14 studies assessed the rosuvastatin preloading and the pooled estimates demonstrated a significant reduction in MACCEs following rosuvastatin preloading amongst patients undergoing PCI (nearly 60% reduction). A similar finding was reported on female patients with acute coronary syndrome[22–24] and non-STEMI[25]. We hypothesize that this heterogeneity within the published literature stems from the inclusion of various types of acute coronary syndrome, wide variability in patients' characteristics and operators' experience, and variations in the duration of follow-up and definition of clinical outcomes.

CI-AKI is a relatively frequent, sometimes serious, complication of PCI that may lead to a significant increase in hospital stay, excessive healthcare expenditure, high risks of short/long-term complications, and even morality[26]. Previous reports demonstrated that up to one-third of the patients affected by CI-AKI are at increased risk of persistent deterioration in renal functions[27]. Besides, the development and progression of CI-AKI appear to be correlated with the degree of deterioration in renal functions[28]. Thus, various prophylactic measures were proposed in patients undergoing PCI such as intravenous hydration and lowering the dose of contrast agents[29]. Statin is a potential prophylactic agent for CI-AKI due to its anti-inflammatory and anti-oxidative function, which can exert a nephroprotective effect, with conflicting clinical results[30,31]. In the present trial, we demonstrated serum creatinine was significantly lower in the rosuvastatin group than the control group; which highlights that rosuvastatin preloading before PPCI had renal protective effects and can help in preventing contrast-induced acute kidney injury (CI-AKI). In Leoncini and colleagues' trial, the rosuvastatin preloading was significantly associated with lower incidence of CI-AKI amongst patients undergoing PCI[24].

We acknowledge that this prospective study has some limitations. All patients were recruited from one center only; therefore, these results may not be generalized to all patients. Besides, the small sample size and the lack of long-term follow-up are other limitations.

In conclusion, there is a trend towards better clinical outcomes following a high loading dose of atorvastatin in patients undergoing PPCI. However, this study failed to reach the level of statistical significance. Besides, our results highlighted that rosuvastatin preloading before PPCI had renal protective effects and can help in CI-AKI. Further, well-designed trials are still needed to resolve the controversy within the published literature.

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