The Effect of high loading dose Rosuvastatin before Percutaneous Coronary Intervention in Diabetic Patients with Non-STMI.

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Abstract: Background and objective: Non-STEMI in diabetic patient is a life threatening condition. Many studies have shown the benefit of high dose statin in the management of those patients, loading dose before intervention can improve the outcome but this is not consistent. We aimed to evaluate the effect of high loading dose of rosuavatatin (80mg) in diabetics with Non-STMI on the incidence of 6 weeks major adverse cardiac events and periprocedural myocardial infarction. **Methods:** 100diabeticspresented with Non-STEMI were planned for PCI randomly divided into two equal groups: A high loading dose of rosuvastatin 80 mg for 3 days before PCI, and B 20 mg resuvastatin without loading dose both of them continued on 20 mg rosuvastatin during the period of follow up in addition to traditional treatment according to patient cardiac conditions. Follow up at hospital stay and six weeks after. End points were increase cardiac markers, hs CRP after PCI, and MACE during 1 month (death, Q wave MI, target vessel revascularization, ischemic stroke). **Results:** The results of Lipid profile values, the mean baseline cardiac biomarker (before PCI) & HS-CRP were similar in both groups. Troponin-I levels increased significantly at next morning with higher degree of rise in group B compared to group A. No significant changes in mean values of CK-MB & HS-CRP after PCI in both groups. MACE occurred higher in group B mainly by readmission (24%) due to unstable angina (16%) or due to NSTEMI (8%) compared to group A in whom readmission occurred in (8%) due to UA in (8%), while NSTEMI did not occur. **Conclusion:** high loading dose of rosuvastatin (80 mg) before PCI has cardio-protective effect as it decreased post procedural myonecrosis proved by reducing the degree of rise of troponin-I after PCI, and reduces the incidence of readmission events within the 6 weeks of clinical follow-up.
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Key word: statin, DM, Non-STMI.

1. Introduction:

In patients with non-ST-segment elevation acute coronary syndromes (ACS), the increased plaque inflammatory cell density is observed, with consequently greater local and systemic production of inflammatory markers and cytokines, and elevation of CRP levels. Also in diabetic patients with established CAD, the prognosis is worse in comparison to patients without diabetes. Several mechanisms such as increased state of inflammation, proliferative response to endothelial injury and hypercoagul ability are thought to be partly responsible for inferior outcomes in diabetic patients[1]**.** Even though the prognosis in general has improved with advances in percutaneous coronary intervention (PCI) devices, new stent types and potent antithrombotic treatment, DM is still associated with inferior outcomes[2].

Statins in addition to suppression of cholesterol biosynthesis, reducing the LDL and triglycerides[(3)]**,** exert a number of protective effects involving the improvement of endothelial function, stabilization of atherosclerotic plaque, decrease of oxidative stress and inflammation, and inhibition of thrombogenic response, the so-called pleiotropic effects[(4).] Their benefit has also been largely demonstrated in the setting of PCIs by the prevention of periprocedural myocardial and renal damage [(5)]

The major aetiologies of periprocedural MI include dissection, compromise of side branches due to plaque shifting, thrombosis, distal embolization, and no-reflow phenomenon. However, despite optimal management directed toward mechanical and thrombotic complications, the rate of periprocedural MI is still high, and therapies directed to atherosclerotic and inflammatory processes in the vessel wall may provide additional benefit [(6).]

Despite 80 mg rosuvastatin is not a recommended dose in guideline but **Schneck DW et al.**[7] stated that it is safe dose in management of patients with hypercholesterolemia and without active arterial disease.

As a result of iatrogenic plaque rupture during PCI, besides the risk of mechanical complications, many vasoactive and bioactive substances are released downstream into the microcirculation, leading to vasoconstriction, endothelial dysfunction, myocardial ischemia, and necrosis. These include cholesterol clefts, thrombus, apoptotic bodies, microparticles

derived from platelets and inflammatory cells, oxidized lipids[8], endothelin, angiotensin II, and other factors [9].

Periprocedural myocardial infarction (MI) is generally defined by consensus panels as creatine kinase-myocardial isoenzyme (CK-MB) elevation >3x the upper limit of normal, occurs in 5% to 15% of patients. It has been demonstrated that elevation of CK-MB post-percutaneous coronary intervention (PCI) is associated with increased long-term mortality, with a graded increase in risk according to the extent of elevation. Periprocedural MI is routinely used as an end point in clinical trials and increasingly as a quality performance metric[10].

2. Patients and Methods:

The study included100 diabetic patients who were presented with acute coronary syndrome of unstable angina and NSTEMI, that was planned for PCI in National Heart Institute. These100 diabetic patients were randomly divided (in consecutive pattern) into two groups according to the dose of rosuvastatin received before the PCI, high loading dose of rosuvastatin 80 mg (group A, 50 patients) and non-loading dose of rosuvastatin just start a recommended dose of 20 mg (group B, 50 patients). Group A Received 80mg from the first day of admission for at least 3 days before PCI and then rosuvastatin (20 mg/day) was prescribed where group B 20mg rosuvastatin from the date of admission and continue on the same dose all the time for follow up.

All patients received the traditional treatment of unstable angina and NSTEMI including aspirin, B-blockers, nitrates, low molecular weight heparin and other medications were given according to patient cardiac condition or other co-morbidities.

Inclusion criteria were patients with typical anginal chest pain began in the last 48 hours associated with either transient ST segment depression or dynamic T wave inversion and elevated CKMB & troponin I.

Exclusion criteria were patients with ST elevation myocardial infarction & LBBB, cardiogenic shock, those patients in whom coronary (CABG) was recommended, severe hepatic and renal diseases, high risk acute coronary syndrome in whom early invasive strategy was done, any connective tissue diseases, any inflammatory condition, pregnancy and prior use of statins.

All patients in the study were subjected to full history taking, complete general and local cardiac examinations, echocardiography, resting 12 leads electrocardiography, laboratory investigations including, Plasma lipid profile, Cardiac enzymes including: quantitative troponin-I & CK-MB and High sensitive C-reactive protein titre:(measured on admission and next morning after PCI), Glycated HB (HBA1C) &kidney function test were obtained before PCI.

PCI was performed immediately after diagnostic angiography. In all patients, aspirin (300 mg/day) and clopidogrel (300 mg/day) was given before procedure. An intra-venous bolus of 5000 U of unfractionated heparin was given, and then additional heparin boluses was given to maintain activated clotting time >300s during procedure. Platelet glycoprotein IIb/IIIa inhibitors (GPI) w as administered in both groups. Angiographic success of PCI was defined as TIMI III flow with residual stenosis below 20%. The occurrence of angiographic complications during PCI was recorded such as failed PCI, side branch occlusion, slow or no-reflow, major dissection, and distal embolization. Then Aspirin (81mg/day), clopidogrel (75 mg/day) and rosuvastatin (20 mg/day) was prescribed to all patients after the procedure.

Follow up: The selected patients were followed up at hospital stay and for at least six weeks after PCI to determine (MACE) major adverse cardiac events (death, Q wave MI, target vessel revascularization, ischemic stroke).

Primary end points: (1) The occurrence of periprocedural myocardial infarction that was defined as a post-procedural increase of CK-MB over 3 times higher the normal upper limit in patients with normal baseline enzyme level. In patients with elevated baseline levels of CK-MB, MI was defined as a subsequent increase of more than3-fold in CK-MB from baseline value and an additional increase in second sample, (2) The incidence of no reflow phenomenon in both groups.

Secondary end points: (1) Any post-procedural increase of markers of myocardial injury above upper limit of normal (but not more than 3 folds of upper normal value) or ≥20% increase of elevated baseline value (but not more than3 folds of baseline value), (2) Elevation of hs CRP after PCI, (3) Occurrence of MACE during 1 month (death, Q wave MI, target vessel revascularization, ischemic stroke).

Data Management and Analysis:

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (SPSS 15.0.1 for windows; SPSS Inc, Chicago, IL, 2001). Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

i. Descriptive statistics:

1. Mean, standard deviation (± SD) and range for parametric numerical data.
2. Frequency and percentage of non-numerical data.

ii. Analytical statistics:

1. **Student T** test was used to assess the statistical significance of the difference between two study group means.
2. **Chi-Square test** was used to examine the relationship between two qualitative variables.
3. **Fisher's exact test:** was used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells.
4. **Mann Whitney Test (U test)** was used to assess the statistical significance of the difference of a non parametric variable between two study group.

iii. **P- value: level of significance:** -P>0.05: Non significant (NS). -P< 0.05: Significant (S). -P<0.01: Highly significant (HS).

3. Results:

The range of age was from 34 to 70 years old in group A and from 43 to 73 years old in group B, 44 patients were males & 6 were females in group A and 42 were males & 8 were females in group B,46 patients were hypertensive in group A and 40 patients in group B. And 78 patients were smoker in both groups, 28 patients had previous MI and 26 patients had family history of IHD.

Table (1): Comparison between two study groups as regard personal and medical characteristics.

		Group A		Group B		P-value	Sig.
		N	%	N	%		
Age group	=<55 years	24	48.0%	18	36.0%	0.390*	NS
	>55 years	26	52.0%	32	64.0%		
Sex	Male	44	88.0%	42	84.0%	1.00**	NS
	Female	6	12.0%	8	16.0%		
HTN	No	2	8.0%	10	20.0%	0.417**	NS
	Yes	23	92.0%	40	80.0%		
Smoking	No	4	16.0%	14	28.0%	0.306*	NS
	Yes	42	84.0%	35	72.0%		
Past MI	No	38	76.0%	34	68.0%	0.529*	NS
	Yes	12	24.0%	16	32.0%		
FH (IHD)	No	34	68.0%	40	80.0%	0.333*	NS
	Yes	16	32.0%	10	20.0%		

*Chi-Square Tests. **fisher exact test.

ST segment depression was found in 44 patients (88%) of group A and 22 (44%) T wave changes versus 42 patient (84%) with ST segment depression and 24 patients (48%) of dynamic T wave changes.

Table (2): Comparison between two study groups as regard ECG findings.

ECG changes		Group A		Group B		P-value	Sig
		N	%	N	%		
ST depression	No	6	12.0%	8	16.0%	1.00**	NS
	Yes	44	88.0%	42	84.0%		
Dynamic T- wave inversion	No	28	56.0%	26	52.0%	0.777*	NS
	Yes	22	44.0%	24	48.0%		

*Chi-Square Tests. **fisher exact test. ‡ Student t test.

Lipid profile values were similar in both groups. BMS were used in both groups. The mean baseline values (before PCI) of cardiac biomarkers & HS-CRP were similar in both groups.

Table (3): Showing Comparison between two study groups as regard lipid profile.

	Group A		Group B		P-value	Sig.
	Mean	±SD	Mean	±SD		
TC	234.3	34.4	216.3	43.0	0.110*	NS
LDL	163.6	31.0	146.8	42.1	0.115*	NS
HDL	37.5	5.8	39.0	4.5	0.319*	NS
TG	163.0	50.4	150.1	39.2	0.320*	NS

*Student t test

Table (4): Shows Comparison between two study groups as regard CK-MB, Troponin and hs-CRP level at admission.

	Group A		Group B		P-value	Sig.
	Mean	±SD	Mean	±SD		
CK-MB At Admission	32.64	21.54	52.68	50.99	0.159*	NS
Tropnin at admission	0.10	0.29	0.77	2.18	0.318*	NS
Hs-CRP At Admission	8.81	4.83	10.18	7.09	0.741**	NS

*Mann Whitney test. **Student t test

Troponin-I levels increased significantly at next morning after PCI in group B patients who didn't receive high loading dose rosuvastatin in comparison to group A. No significant changes in mean values of CK-MB & HS-CRP occurred after PCI in both groups.

Table (5): Shows Comparison between two study groups as regard CK-MB, Troponin and Hs-CRP level after PCI.

	Group A		Group B		P-value	Sig.
	Mean	±SD	Mean	±SD		
CK-MB After PCI	43.44	24.80	59.12	44.02	0.337**	NS
Tropnin after PCI	0.33	0.91	3.41	7.32	**0.045****	**S**
Hs-CRP After PCI	17.54	9.68	16.97	13.96	0.377**	NS

****Mann Whitney test**

Major adverse cardiac events occurred higher in group B mainly by readmission (24%) due to unstable angina (16%) or due to NSTEMI (8%) compared to group A in whom readmission occurred in (8%) due to UA in (8%), while NSTEMI did not occur in this group.

Table (6): Shows comparison between two study groups as regard 6 weeks incidence of MACE.

		Group A		Group B		P-value	Sig.
		N	%	N	%		
Readmission	No	46	92.0%	28	76.0%	0.247**	NS
	Yes	4	8.0%	12	24.0%		
UA	No	46	92.0%	42	84.0%	0.667**	NS
	Yes	4	8.0%	8	16.0%		
NSTEMI	No	50	100.0%	46	92.0%	0.490**	NS
	Yes	0	0.0%	4	8.0%		
TVR	No	50	100.0%	48	96.0%	1.00**	NS
	Yes	0	0.0%	2	4.0%		
MACE	No	46	92.0%	36	72.0%	0.138**	NS
	Yes	4	8.0%	14	28.0%		

**Fisher exact test

From all these mentioned results it appeared that high loading dose of rosuvastatin had a beneficial role in myonecrosis reduction after PCI if given immediately on admission in diabetic patients with UA or NSTEMI.

4. Discussion:

Large periprocedural myocardial infarction are usually due to angiographically visible complications (epicardial side-branch occlusion or to the damage of the microvascular circulation) however, this is not the case of the majority of patients with elevated biomarker levels after PCI[(11)]. Detection of the periprocedural myocardial necrosis can be done by quantitative measurement of myocardial enzymes and structural proteins such as creatine kinase-myocardial band (CK-MB) and troponins (Tn). Elevation of cardiac biomarkers above the 99th percentile upper limit of normal after PCI is an indicator of peri-procedural myocardial necrosis [(12).] In addition to periprocedural myonecrosis during PCI, Vascular injury also occurs and is associated with increase in serum CRP concentration follows the increase in serum IL-6 concentration by 12–36 hrs., reaching its peak value by 24 hrs. after the procedure and this increase was found to be correlated with post-procedural troponin T elevationand increase cardiovascular risk[(13)].

In stable clinical situations, it is thought that statins mediate their primary benefit via LDL reduction. However, in acute situations (such as acute coronary syndromes or coronary interventions), pure LDL reduction cannot explain cardiac protection [(14).] In setting of ACS patients; numerous benefits beyond lipid-lowering were reported for acute-stage ACS management using intensive statin therapy. Furthermore, many studies demonstrated the efficacy of statins in avoidance of periprocedural myocardial injury because of their pleiotropic effect[(15)]. It has been shown that administration of statins treatment before endothelial injury during coronary procedures, likely mitigates the inflammatory cascade by decreasing vascular reactivity and stabilizing plaque, both at the site of intervention and at other "vulnerable" lesions. These biological effects are thought to be the basis of periprocedural statins myoprotection [(14).] The anti-inflammatory role of statins could be explained by increasing nitric oxide bioavailability, and with its inherent antioxidant properties and stabilize atherosclerotic plaques. Furthermore it is shown that pleiotropic effects of statins may occur immediately after a single dose of statins[(16).] Moreover, earlypleiotropic effects of statins, including antithrombotic action, improvement of coronary flow velocity reserve by vasodilation of coronary microvessels and rapid (12 hrs. after a single dose of atorvastatin) improvement of endothelial function [(17)].

Yun et al., [13]found in his study that included 455 patients with ACS who underwent PCI who were randomly assigned either no statin group (CG) and high single dose rosuvastatin 40 mg group (RG), that peak value of all markers were elevated after PCI significantly higher in control group. That is, CK-MB changed from 28±30 to 35± 27 IU/L in control group and from 27± 27 to 30±25 IU/L in RG. Troponin T changed from 0.2±0.6 to 0.5±1.0 ng/mL in CG, from 0.2±0.7 to 0.3±0.5 ng/mL in RG.

These results are in agreement with our study where mean baseline values of CK-MB & Troponin-I before PCI were similar whereas after PCI peak values of troponin-I changed by a rate significantly higher in control group than in rosuvastatin group(2.64 vs 0.23 respectively). In spite that peak value &rate of change of CK-MB after PCI was higher in CG than in RG (10.80 vs 6.44) respectively but that was statistically insignificant between both groups on contrary to **Yun et al., study[13].**

Also it is noted in our study that the rate of change of troponin was more significant between both groups than **Yun et al.,** [13] that may be due to difference in dose of rosuvastatin dose (single dose vs 3 high doses 40 mg in our study).

Regarding the inflammatory response following PCI **(Yun et al.,** [13]**)**, found that the rate of change of hs-CRP was significantly higher in CG than RG (8.74 vs 6.79 respectively) which in disagreement with our study where the rate of change of hs-CRP was statistically insignificant between both groups. This discrepancy between both studies might have been due to small study sample & possibly due to exclusion of early invasive patients (rescuer patients) where the inflammatory status is expected to be more pronounced.

Sardela et al., [16] published a randomized study to assess cardio-protective effects of single dose rosuvastatin 40 mg in patients with stable angina underwent elective PCI, they found the occurrence of 6hrs. CK-MB elevation >3 times of ULN was (2.3% in CG versus 1.4% in RG) and twelve and 24-hr post-PCI myonecrosis occurred more frequently in the CG than in the RG. TnT elevation >3 ULN measured at 6, 12, and 24 hrs, occurred significantly more frequently in CG than in RG patients: (30.4% vs. 6.9%), (65.2% vs. 25.0%) and (69.6% vs. 37.9%) respectively. hs-CRP was not assessed in this study.

In spite that our results regarding troponin peak values after PCI was in harmony with **Sardela et al.,**[16] study but we measured troponin & CK-MB values only after 12 hrs (next morning after PCI (for financial reasons) and that decreased the accuracy of strict assessment of myocardial biomarkers fluctuation following PCI.

Also, our findings were in harmony with **Yuan et al.,** [18] study that included 117 female patients with NSTEMI/UA who were randomly assigned to either the group of rosuvastatin (20 mg 12 hrs. preprocedure & 10 mg 2 hrs. before PCI procedure) or the no rosuvastatin treatment group before PCI. They found that the incidence of periprocedural myocardial injury was higher in non-loading than loading dose group (CKMB: 10.17% vs. 25.86%; Troponin I: 11.86% vs. 29.31%).

Regarding beneficial effect on MACE; **Yun et al.,** [13] found that in patients who were received rosuvastatin loading prior to PCI had a lower incidence of 30 day MACE compared to the patients who have not taken statin before PCI (15.9% vs. 6.7%). The different outcomes mainly resulted from the higher incidence of periprocedural MI in control group.

In our study, rate of Major adverse cardiac events (MACE) a 6 weeks were higher in group II (28%) compared to group I (8%) however this difference was statistically insignificant. this may refer mainly to readmission (24%) by unstable angina (16%) or readmission due to NSTEMI (8%)compared to group I in whom readmission occurred in (8%) due to UA while NSTEMI did not occur in this group meanwhile;

Target vascular revascularization occurred in 1 patient (4%) in group II however this difference was statistically insignificant.

The more significant decline in the rate of MACE in **Yun et al.,**[13] study may be explained by the very large study sample compared to our study**.**

As regard other studies demonstrated efficacy of high loading dose of statins before PCI using other statins rather than rosuvastatin used in our study; ‘‘**ARMYDA** (Atorvastatin for Reduction of Myocardial Damage During Angioplasty)’’ was the first randomized, placebo-controlled study, evaluating the effects of 7-day therapy with 40 mg/day of atorvastatin on postprocedural myonecrosis in patients with stable angina undergoing PCI that was associated with an 80% risk reduction in the occurrence of periprocedural myocardial infarction, as well as with a significant reduction in post intervention peak levels of all markers of myocardial damage [19]**.**

The **ARMYDA-ACS trial** was the first randomized study to assess the efficacy of high dose statin loading therapy before PCI in patients with ACS. The results of this trial indicated that 80 mg atorvastatin loading at 12 h before PCI reduced post-procedural biomarker elevation and 30-day MACE [20]**.**

Moreover, **Briguori et al.,** [21] published a randomized study to assess the cardio protective effects of statins administration 3 days before elective PCI in stable patients. In this study, the incidence of a large non-Q wave myocardial infarction was 8.0% in the statins group and 15.6% in the CG. The authors used a different variety of statins (atorvastatin, pravastatin, simvastatin, and fluvastatin).

Patti et al., [20] published a meta-analysis of several randomized trials to demonstrate efficacy of statin treatment before invasive procedure (ACS and stable angina). The authors found that periprocedural MI occurred in 7.0% of patients in the high-dose statin pretreatment group versus 11.9% of those in the CG. The rate of major adverse cardiac events at 30 days and 1- month was significantly lower in the high-dose statin group. In particular, statin therapy was initiated ~12 hrs. to 7 days before PCI, and the majority of included PCI studies had a follow-up of 30 days.

5. Conclusion:

This randomized study supports the cardio-protective effect of a high loading dose of rosuvastatin (80 mg) administered before PCI as aggressive & intensive dose of rosuvastatin decreased post procedural myonecrosis via reducing the degree of rise of troponin-I after PCI, also High loading doses of rosuvastatin before PCI reduced the incidence of MACE mainly by reduction of periprocedural readmission events within the 6 weeks of clinical follow-up (despite it was statistically insignificant in our small study size).

Limitations of the Study:

The major limitation of this study is the limited sample size, we measured troponin & CK-MB values only at 12 hrs. following PCI, other more specific anti-inflammatory markers as interleukins, tumour necrosis factor-α were not evaluated in this study, the clinical follow up was only done without laboratory assessment of cardiac biomarkers or hs-CRP and long term benefits of loading dose of rosuvastatin in reduction of MACE at 6 & 12 months clinical follow up were not evaluated in our study.

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