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Loading Dose of Rosuvastatin Before PCI and its Beneficial Post-Procedural Effects: A Systematic Review

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Loading Dose of Rosuvastatin Before PCI and its Beneficial Post- Procedural Effects: A Systematic Review

Abstract

Background: Many patients with acute coronary syndrome in the United States electively choose to undergo percutaneous coronary angioplasty. One of the many risks associated with this procedure is peri-procedural myocardial infarction (MI). Recently, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors otherwise known as statins administered before the procedure have been shown to reduce the incidence of peri-procedural myocardial infarction. Many of the studies that have been done have used atorvastatin and have been limited to peri-procedural outcomes. Will administering a loading dose of rosuvastatin before percutaneous coronary intervention (PCI) improve mid and long term outcomes?

Methods: An exhaustive search of available medical literature was conducted using Medline-OVID, EBSCO, CINAHL, Health Source-Consumer, and Web of Science using the keywords: rosuvastatin and percutaneous coronary intervention. Relevant articles were assessed for quality using GRADE.

Results: Three studies, with one including a 12-month follow up study met inclusion criteria. A prospective randomized trial of 445 patients that included a 12-month follow up study concluded that a 40mg loading dose of rosuvastatin before PCI improved 12-month clinical outcomes. A single center, prospective, randomized trial of 160 patients demonstrated that a 40mg loading dose of rosuvastatin before elective PCI decreased the incidence of postprocedural MI during a period of 12 months compared to standard treatment. A randomized, prospective, double-blind, placebo-controlled trial of 125 patients concluded that a 20mg loading dose of rosuvastatin before PCI reduces the incidence of postprocedural MI in patients with acute coronary syndrome.

Conclusion: A loading dose of rosuvastatin has been shown to reduce the incidence of both myocardial infarction and major adverse cardiac events up to 12 months post-procedure. More research is needed to discover the exact mechanism of action. Furthermore, more research is needed to address the correct dosing, timing of administration, and whether or not rosuvastatin is better than other statins in the setting of PCI. Lastly, can patients with ST-elevation myocardial infarctions undergoing PCI benefit from the same treatment?

Keywords: Rosuvastatin and percutaneous coronary intervention

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**Loading Dose of Rosuvastatin Before PCI and its Beneficial
Post-Procedural Effects: A Systematic Review**

Andrew Ravella Galli



A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 2014

Faculty Advisor: Dr. Mark Pedemonte

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS

Biography

Andrew Ravella Galli is a native of the San Francisco Bay Area. He majored in Sociology at California State University East Bay. While completing his undergraduate degree, he spent one year living abroad in Italy to gain more understanding of his roots. After finishing his undergraduate degree, he was chosen to participate in a one-year internship as a Firefighter/Emergency Medical Technician in Redwood City, California. This was where he first gained interest in the medical field. Due to his newfound interest in medicine he sought out and gained employment at two hospitals, as an Electrocardiograph Technician and an Emergency Room Technician. He then pursued additional coursework in Biology in order to gain acceptance at Pacific University School of Physician Assistant Studies.

Abstract

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To my parents: Thank you for always supporting me through thick and thin. You guys are the best.

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Table I: Characteristics of Reviewed Studies as well as the Summary of Findings

List of Abbreviations

ACS.....Acute Coronary Syndrome
PCI.....Percutaneous Coronary Intervention
MI.....Myocardial Infarction
CABG.....Coronary Artery Bypass Graft
GRADE..... Grading of Recommendations, Assessment, Development and Evaluations

Loading Dose of Rosuvastatin Before PCI and its Beneficial Post- Procedural Effects: A Systematic Review

BACKGROUND

Approximately 1.4 million patients undergo percutaneous coronary intervention (PCI) in the United States every year.¹ Many of these patients are at risk of peri-procedural myocardial infarction (MI).² Ensuing major post-procedural adverse cardiac events such as death and MI are related to the amount of cardiac enzymes that are released during the injury.^{3,4}

Three-hydroxy-three-methylglutaryl coenzyme A reductase inhibitors, otherwise known as statins, have been used for many years in the medical field to reduce the amount of LDL cholesterol in humans. Many studies^{5,6} have demonstrated the beneficial effects statins have on morbidity and mortality. Recently these beneficial effects have been thought to stem from not only the cholesterol lowering action but also the so called pleiotropic effects of statins. These pleiotropic properties include beneficial effects on endothelial function, enhancing the stability of atherosclerotic plaques, inhibiting vascular smooth muscle proliferation, and reducing vascular inflammation.⁷ This can be seen in the new guidelines put out this November by the American Heart Association and the American College of Cardiology. In the new guidelines,^{8,9} cholesterol levels do not matter anymore, it is all about risk.^{8,9} Due possibly to their pleiotropic effects, statins are now the drug class being looked at for controlling these risks.

In recent years, studies have confirmed that statin administration before PCI reduces peri-procedural MI's in patients with stable angina.^{5,6,10} Most of these landmark studies used atorvastatin and were limited to peri-procedural outcomes.^{5,6,10} Does

administering a loading dose of rosuvastatin before undergoing percutaneous coronary intervention improve postprocedural outcomes in patients with acute coronary syndrome or stable angina? If it does improve outcomes, how are these mid and long term outcomes affected?

METHODS

An exhaustive search of available medical literature was conducted using Medline-OVID, EBSCO, CINAHL, Health Source-Consumer, and Web of Science using the keywords: rosuvastatin and percutaneous coronary intervention. Eligibility criteria was met by the study being done on humans, published in English, and by containing data on post-procedural outcomes defined by a minimum of at least 24 hours post percutaneous coronary intervention (PCI). Included studies were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).¹¹

RESULTS

The initial result of the search yielded 85 articles for review. After screening relevant articles for the inclusion criteria, a total of 4 articles remained. These articles consisted of three randomized controlled trials¹²⁻¹⁴ and a 12-month¹⁵ follow up to one of the trials. See Table I.

Yun et al

This prospective randomized study¹² that included a 12-month follow up study¹⁵ investigated the effect of administering a high loading dose of rosuvastatin on patients with non-ST-segment elevation acute coronary syndrome (ACS) before PCI. The trial enrolled 445 adult patients with non-ST-segment elevation ACS that received diagnostic

coronary angiography. The primary endpoint was the occurrence of peri-procedural myocardial infarction (MI). The secondary endpoints included 1) any post-procedural increase in markers of myocardial injury above upper limit of normal or greater or equal to 20% increase of the baseline value, 2) peak values of high-sensitivity c-reactive protein (hsCRP) after PCI, and 3) occurrence of major adverse cardiac events (MACE) during the first 30 days up to 12 months. MACE was defined as death, Q wave MI, target vessel revascularization, and ischemic stroke.^{12,15}

Eligibility criteria consisted of patients with non-ST-segment elevation ACS that received diagnostic coronary angiography. Exclusion criteria consisted of prior use of statins, cardiogenic shock, those in which medical treatment was recommended, those in which coronary artery bypass graft (CABG) was recommended, and those with severe hepatic or renal diseases. The 445 patients who met the criteria were then randomized by a 1:1 ratio into two groups. There were 220 patients in the control group and 225 patients in the rosuvastatin group. One group did not receive rosuvastatin (control group) and the other group received 40mg of rosuvastatin (rosuvastatin group) before PCI. Both groups did receive 300mg of aspirin and 300mg of clopidogrel before the procedure.^{12,15} Post-procedurally both groups also received 200mg of aspirin, 75mg of clopidogrel, and 10mg of rosuvastatin daily. Statistical difference was not found between the two groups' baseline characteristics.^{12,15}

Rosuvastatin administration prior to PCI was found to significantly reduce the incidence of myocardial infarction, 30 day MACE, and MACE at 12 months. Myocardial infarction was detected after PCI in 5.8% of those in the rosuvastatin group and 11.4% of the patients in the control group (P=0.035). Moreover, patients who received rosuvastatin

loading prior to PCI had a lower incidence of 30 day MACE compared to the control group (6.7% vs. 15.9%, P=0.002, respectively).^{12,15} Furthermore, rosuvastatin loading before PCI was also shown to reduce MACE at 12 months. Multivariate analysis revealed that rosuvastatin loading (OR = 0.5; 95%CI =0.3-0.8, P=0.006) was the independent predictor for decreased risk of 12-month MACE.^{12,15}

The authors did find some limitations of this study. They cited the fact that their study was not blinded, and their sample size was small. The authors did express the need for more research to confirm their results. The authors did conclude that their study does support the use of high dose rosuvastatin loading therapy before PCI in patients with ACS.^{12,15}

The ROMA Trial

This single center, prospective, randomized trial¹³ set out to assess whether a single, high loading dose of rosuvastatin is effective in reducing the post-procedural elevation of cardiac biomarkers after elective, non-urgent coronary angioplasty. The study enrolled 160 adult patients. The primary endpoint of the study was the incidence of peri-procedural MI. This was defined as CK-MB elevation above 3 times upper limit of normal or any CK-MB elevation associated with chest pain, ST-segment, or T-wave abnormalities in patients undergoing non-urgent PCI. The secondary endpoint was the incidence of major adverse cardiac and cerebrovascular events (MACCE). They defined MACCE as cardiac death, peri-procedural MI, spontaneous MI, target vessel revascularization, and stroke.¹³

The inclusion criteria for this study was age greater than 18, elective PCI due to symptomatic coronary artery disease, and “de novo” lesions in a native coronary artery,

baseline cardiac enzymes had to be within normal limits, and no previous statin therapy. Exclusion criteria consisted of ACS with elevated cardiac enzymes, primary or rescue PCI, renal failure, previous MI, left ventricular ejection fraction of less than 30%, elevated liver enzymes, and inability to give consent.¹³

The day before the procedure the 160 eligible patients were randomly assigned into two groups. The randomization was done by a 1:1 ratio using computer-generated random numbers. Statistical prognostic difference was not found between the two groups. One group would receive 40mg of rosuvastatin within 24 hours of PCI (rosuvastatin group) and the other group would not receive the rosuvastatin (control group). Both groups would receive 300mg of clopidogrel, and 500mg of aspirin 24 hours before the procedure. Post-procedurally both groups were put on a regime of aspirin, clopidogrel, and 20mg of rosuvastatin.¹³

Rosuvastatin administration prior to PCI was found to significantly reduce the incidence of peri-procedural MI as well as overall MACCE. Peri-procedural MI was the main difference between the two groups (8.7% vs. 26.4%; P = 0.003, respectively). The study also showed that at 30 days and 12 months the rate of overall MACCE was substantially lower in the rosuvastatin group compared to the control group (8.7% vs. 30%; P = 0.001 and 12.5% vs. 35%; P = 0.001 respectively). Moreover, multivariate analysis showed that pretreatment with rosuvastatin significantly reduced the risk of overall MACCE (hazard ratio 0.124, 95% CI 0.041 to 0.292; P = 0.022).¹³

The limitation of the study pointed out by the authors was mainly the fact that their study was not blinded.¹³ The authors did state that their study does support the

cardioprotective effect of a single high (40mg) loading dose of rosuvastatin administered within 24 hours before stent implantation.¹³

Wang et al

This randomized, prospective, double-blind, placebo-controlled trial¹⁴ was set up to investigate whether pre-treatment with rosuvastatin can reduce procedural myocardial damage in patients with ACS undergoing elective PCI. The study enrolled 125 adult patients. Exclusion criteria was a previous history of statin treatment, current cardiogenic shock, patients in whom medical management was recommended, those in whom coronary artery bypass graft was recommended, and patients that had severe hepatic or renal disease.¹⁴

The primary endpoints included major adverse cardiac events (MACE) that occurred within 30 days after PCI. These included cardiac death, MI, and target artery revascularization. The secondary endpoint was an elevation in cardiac markers above the upper normal limit within 30 days post PCI.¹⁴

The 125 eligible patients were randomly assigned to either receive a 20mg loading dose of rosuvastatin 2 to 4 hours before PCI (rosuvastatin group) or to receive the placebo treatment (control group). Randomization was performed in a 1:1 ratio. Furthermore, physicians performing the procedure were blinded to the randomization assignment.¹⁴ Statistical prognostic difference was not found between the two groups. Both groups, however, did receive 100mg of aspirin and 75mg of clopidogrel daily, with a total dose of at least 300mg before PCI. After the procedure both groups were treated with low-molecular weight heparin for 3 to 5 days, 75mg of clopidogrel a day for at least

12 months, 10mg of rosuvastatin every night for at least one month, and 100mg of aspirin a day for as long as possible.¹⁴

A loading dose of rosuvastatin was found to drastically reduce the amount of all cause MACE at 30 days post PCI. MACE, which was defined as cardiac death, MI, and target vessel revascularization occurred in 8.1% (5 of 65) of the rosuvastatin group and 22.2% (14 of 63) in the control group (P <.01). More importantly the incidence of MACE at 1 month was completely influenced by postprocedural myocardial infarction (8.1% vs. 22.2% P <.01, respectively).¹⁴

The authors do not cite any specific limitations, although one cannot overlook their small sample size. The authors do state that a high loading dose of rosuvastatin before PCI may reduce postprocedural MI in patients with ACS. They believe it is due to the inhibition of inflammatory markers. They do state the need for more studies to clarify the involved mechanisms.¹⁴

DISCUSSION

Many studies^{5,6,10,16} have touted the beneficial effects of administering a statin loading dose to patients before percutaneous coronary intervention (PCI). The atorvastatin for reduction of myocardial damage during angioplasty study (ARMYDA Trial)¹⁰ found that pretreatment with atorvastatin 40mg daily for 7 days significantly reduces procedural myocardial injury in elective coronary intervention.¹⁰ The ARMYDA-ACS trial⁶ found that an 80mg loading dose of atorvastatin 12 hours before PCI in patients with non-ST-segment elevation ACS improved outcomes. The NAPLES II trial¹⁶ found that pre-procedural statin therapy reduces the incidence of large non-Q-wave myocardial infarction after PCI.

This systematic review demonstrates that a 20 to 40mg loading dose of rosuvastatin within a time period of 2 to 24 hours before PCI significantly reduces major adverse cardiac events at 30 days and up to 12 months in statin naïve patients with ACS or stable angina undergoing PCI. While a majority of the cause of MACE at 30 days and 12 months was due to the reduction in peri-procedural myocardial infarction, it is still important to note that rosuvastatin still shows beneficial outcomes up to 12 months post PCI. Due to the fact that most of the landmark trials^{5,6,10} in this setting used atorvastatin, many providers are not currently using rosuvastatin. Many providers use atorvastatin even though rosuvastatin has outperformed atorvastatin in improving lipid profiles in patients with ACS.¹⁷

One general statement that needs to be made is that even though all of the studies¹²⁻¹⁵ cited a small sample size as a limitation, the treatment effect was large which estimates that rosuvastatin is still likely to be beneficial. However, these studies¹²⁻¹⁵ do contain some limitations. One limitation of these studies is that they did not address the optimal dose. Another limitation is that they did not discuss the amount of time needed between administering rosuvastatin and the procedure. Moreover, the specific “statin naïve” patient population all of these studies employed limits the generalizability of the results of these studies. Lastly, two of the studies^{12,13,15} were not blinded.

CONCLUSION

Rosuvastatin has been demonstrated as a safe and effective medication to reduce the incidence of peri-procedural myocardial infarction as well as major adverse cardiac events in this specific patient population up to 12 months post PCI. The overall combined quality of the articles using the GRADE criteria is a score of high moderate. This was due

to the studies having a large treatment effect. While many studies have made clear the fact that administering a loading dose of a statin before PCI improves outcomes, many questions still remain. Is atorvastatin more effective than rosuvastatin in this setting? Is statin loading beneficial in patients that present with an ST-segment elevation myocardial infarction? Are the beneficial outcomes due to the pleiotropic effects of statins? Many more studies need to be done to answer these questions.

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TABLE 1 Characteristics of Reviewed Studies, GRADE profile

Quality Assessment							Summary of Findings					Importance	
No. of Studies	Design	Downgrade Criteria					Study	Number of Patients		Effect			Quality
		Limitations	Indirectness	Imprecision	Inconsistency	Publication bias likely		Treatment (total)	Placebo or no treatment (total)	Relative Risk	NNT		
Major Adverse Cardiac Events (MACE) at 30 Days													
3	3 RCT	Serious Limitation _a	No serious indirectness	No serious imprecision	No serious inconsistencies	Likely bias _b	Yun et al ^{12,15}	3 (225)	13 (220)	0.226	22	High Moderate	Critical
							Sardella et al ¹³	7 (80)	24 (80)	0.292	5		
							Wang et al ¹⁴	5 (62)	14 (63)	0.363	8		
Major Adverse Cardiac Events (MACE) at 12 months													
2	2 RCT	Serious Limitation _a	No serious indirectness	No serious imprecision	No serious inconsistencies	Likely bias _b	Yun et al ^{12,15}	19 (225)	32 (206)	0.544	15	High Moderate	Critical
							Sardella et al ¹³	10 (80)	27 (80)	0.37	5		
Myocardial Infarction at 30 days													
3	3 RCT	Serious Limitation _a	No serious indirectness	No serious imprecision	No serious inconsistencies	Likely bias _b	Yun et al ^{12,15}	2 (225)	5 (220)	0.391	73	High Moderate	Critical
							Sardella et al ¹³	7 (80)	21 (80)	0.333	6		
							Wang et al ¹⁴	5 (62)	14 (63)	0.363	8		
Elevated CK-MB levels at 24 hours post-procedure (defined as 3 x Upper Limit of Normal)													
2	2 RCT	Serious Limitation _a	No serious indirectness	No serious imprecision	No serious inconsistencies	Likely bias _b	Sardella et al ¹³	7 (80)	21 (80)	0.333	6	High Moderate	Important
							Wang et al ¹⁴	12 (62)	22 (63)	0.554	7		

^aNo blinding in the Yun et al study^{12,15} as well as in the Sardella et al study¹³

^bSardella et al study¹³ contained a likely risk for selection bias because it was conducted in just one medical center

