Hormozgan Medical Journal
Vol 21, No.4, Oct-Dec 2017
DOI:10.29252/hmj.21.4.218

High and low dose atorvastatin effects on high sensivity C-reactive protein in patient with acute coronary syndrome

Ahmadnoor Abdi [1] Shafei Rahimi [2] Hossein Farshidi [1] Vahid Vahdat Khah [3] Elham Boushehri [4]

[1] Department of Cardiology, Cardiovascular Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.
[2] General Physician, Cardiovascular Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.
[3] Specialist in Internal Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.
[4] Department of Medical Education, Faculty of Health, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.

Received 6 June, 2017 Accepted 24 Dec, 2017

Original Article

Abstract

Introduction: The effect of statins in reducing the risk of acute cardiovascular events is not only due to their effect on serum cholesterol level but also from their anti-inflammatory effects, particularly those resulting from reducing of C - reactive protein (CRP), is important. Atorvastatin dose and duration of treatment display different effects. This study compared the effects of high and low doses atorvastatin in reducing serum level of high sensitivity C reactive protein (hs-CRP).

Methods: One hundred patients with unstable angina or Non ST Elevation Myocardial Infarction (NSTEMI) randomized into two groups. Group 1 (n=50) received atorvastatin 80, 20 and 20 mg in three days but group 2 (n=50) received atorvastatin 80 mg/day for three days. High sensitivity C-Reactive protein was measured at admission time and after three dose atorvastatin therapy.

Results: Hs-CRP significantly decreased from baseline to end of three doses treatment in both groups (P=0.0001). However, the reduced level was greater in the group2 than group1 (-39.5% vs -31.2%, P=0.0185).

Conclusion: We found that both treatment methods have significantly effect on hs-CRP in short term but high dose (80 mg/day) atorvastatin being associated with significantly greater reductions in hs-CRP concentration.

Correspondence:
Hossein Farshidi, MD.
Cardiovascular Research Center, Shahid Mohammadi Hospital, Hormozgan University of Medical Sciences.
Bandar Abbas, Iran
Tel:+98 9177688978
Email:
hos_farsh@yahoo.com

Key words: Atorvastatin, Acute Coronary Syndrome, CRP, NSTEMI

Citation: Abdi A, Rahimi Sh, Farshidi H, Vahdat Khah V, Boushehri E. High and low dose atorvastatin effects on high sensivity C-reactive protein in patient with acute coronary syndrome. Hormozgan Medical Journal 2017;21(4):194-199.

Introduction:

Coronary artery disease (CAD) is leading cause of death worldwide. The main pathology for CAD is atherosclerosis that known as a chronic inflammatory phenomenon. Acute Inflammatory response play an important role in the onset and development of acute events (1-3). Atherosclerotic plaques which contain more inflammatory cells are more prone to rupture (4). These plaques known as vulnerable plaques. Reduction in serum concentrations of inflammatory marker decrease acute coronary events in both patients with or without history of CAD (2). C- reactive protein (CRP) is involved in atherosclerotic processes so that increased CRP levels may increase the risk of

coronary events (2,5-9). High Sensitivity C-Reactive Protein (hs-CRP) is one of the predictive factors for risk of acute coronary events (1,3,5,8).

Therefore CRP is one of the best markers available for inflammation evaluation in patients with CAD (3,7,10) hs-CRP level may use for stratifying patients to higher and lower risk groups. Elevated hsCRP levels in patients with acute coronary syndrome (ACS) show higher risk of recurrent events (8). Also LDL and oxidized LDL level has prognostic information but increased hs-CRP levels indicate a worse prognosis in patients with ACS (11,12).

Effect of statins in decreasing coronary event is not only due to decreasing cholesterol level but its anti-inflammatory effect is an important factor in these patients (13,14).

Atorvastatin is one of the statins drug groups that used widely in prevention and treatment of patients with ACS. Atorvastatin effects on hs-CRP serum level is dose dependent (5,14) and high dose being associated with greater reductions in hs-CRP concentrations (5). At the same time other studies showed that early treatment with low dose atorvastatin modifies inflammatory response after one week (15). It means that positive effect of low dose atorvastatin treatment can be achieved with long time of treatment duration. In patients with ACS, treatment with 10,20,40 and 80 mg of atorvastatin has controversial anti-inflammatory effect but this effect was independent of the change in cholesterol level (5,15-17]. A study from China in patients with hypercholestrolemia showed cholesterol lowering effect of statins with no significant effect on hs-CRP (18). There are general agreement that statins effects the hs-CRP and result in decreasing attacks of ACS but still there are doubt about the best recommended dose and duration of treatment to be continued (19). In the present study we compared the effect of short term high and low dose atorvastatin treatment on hs-CRP level in patients with ACS.

Methods:

This trial was a Single blind-Randomized-Prospective study that was carried out on patients admitted with Unstable Angina or NSTEMI in Shahid Mohammadi hospital (General educational medical center, Bandar Abass-Iran). 100 patients were included in our study by simple randomized sampling.

Exclusion criteria included ST Elevation Myocardial Infarction, diabetes mellitus, heart Failure, renal failure, uncontrolled hypertension, active infectious diseases, current use of statins, fibrates and other lipid lowering therapy, use of aspirin and other NSAID (nonsteroidal anti-inflammatory drug).

Patients were randomized in 1:1 manner into two treatment groups: group 1) 80mg atorvastatin at first day and continue with 20mg for two next days. Group 2) 80mg/day atorvastatin for three days.

We used a High Sensitivity assay for measurements of serum C- reactive protein (hs-CRP) with Immunoturbidometry method. For all patients, hs-CRP was assayed at admission and after treatment by three doses of atorvastatin.

All patients were treated with ACE inhibitors, heparin, aspirin, nitrates, beta blockers, (according to the American Heart Association guideline). The protocol was approved by the Research Ethics Committee. All patients gave written informed consent before entering the study.

Statistical analysis was performed by Epi Info for windows (V.3.5.3-2011). Continuous variables were expressed as mean±SD. Comparison of variables between groups was performed using the Chi-square test and unpaired t-test. P-values of <0.05 were considered statistically significant.

Results:

One hundred patients (58 males, 42 females) with an average age of 62.3±10.9 years were include in this study. Baseline characteristics did not differ between the two groups (Atorvastatin 80-20-20mg and Atorvastatin 80-80-80 mg) (Table 1).

In both groups, the baseline hs-CRP levels were comparable (0.64±0.96 vs 1.44±3.11 mg/dl, P=0.0866) also at the end of 3 doses treatment were comparable (0.44±0.72 vs 0.87±2.07 mg/dl, P=0.1741). Hs-CRP significantly decreased from baseline to end of 3 doses treatment in group 1 (P=0.0001) as well as in group2 (P=0.0001) (Figure 1). However, the decrease was greater in the group2 than group 1 (-39.5% vs -31.2%, P=0.0185) (Table 2).

Table 1. Baseline characteristics

		Group 1 (80, 20, 20 mg)		Group 2 (80, 80, 80 mg)		P-value*
		N=50	%	N=50	%	
Age (Mean±SD)		62.4±11.1		62.3±10.8		0.9710
Gender	**Male**	32	64	26	52	0.1555
	Female	18	36	24	48	
History of	**Chronic hear disease**	30	60	25	50	0.2107
	Hypertension	21	42	19	38	0.4192
	Hyperlipidemia	1	2	0	0	0.5
	Stroke	3	6	1	2	0.3086
	Smoking	25	50	17	34	0.0778

* P-values of <0.05 were considered statistically significant

Table 2. Change of means and median of hs-CRP concentration after atorvastatin therapy

	Mean hs-CRP (mg/dl)		Median hs-CRP (mg/dl)		P-value
	Group 1 (80, 20, 20 mg)	**Group 2 (80, 80, 80 mg)**	**Group 1 (80, 20, 20 mg)**	**Group 2 (80, 80, 80 mg)**	
Admission time	0.64±0.96	1.44±3.11	0.3 (0.1, 6.1)	0.6 (0.01, 21.2)	0.0866
After 3 dose therapy	0.44±0.72	0.87±2.07	0.2 (0.01, 4.5)	0.3 (0.01, 14)	0.1741
Change (%)	-0.20±0.26 (-13.2%)	-0.57±1.06 (-39.5%)	-0.1 (-1.6, 0.1) (-33.3%)	-0.3 (-7.2, 0) (-50%)	0.0185
P-value**	0.001	0.0001			

* P values of <0.05 were considered statistically significant
* P-value, group1 vs. group2
** P-value, After 3 dose therapy vs. Admission time

Table 3. Results of atorvastatin effect on CRP level in other studies

Study	Dose (mg/day)	Duration therapy	Reducing (%)
Ostad (18)	80	8 weeks	61.2
Naser Hossein (7)	80	6 months	40
Recent study	80	3 day	39.5
Bonnet (5)	80	5 weeks	36.4
Gensini (1)	80	12 weeks	33.6
Recent study	80 (80 mg intitially and continue 20 mg/day)	3 day	31.2
Macin (6)	40	1 month	84
Macin (6)	40	Discharge time (4±3 days)	62
Naser Hossein (7)	40	6 months	30
Gensini (1)	40	12 weeks	23.1
Karaca (16)	20	4 weeks	47
Keles (17)	20	1 month	37
Keles (17)	20	3 months	36
Gensini (1)	20	12 weeks	28
Keles (17)	20 (every other day)	3 months	25.6
Keles (17)	20 (every other day)	1 month	21
Naser Hossein (7)	20	6 months	20
Bonnet (5)	10	5 weeks	25
Gensini (1)	10	12 weeks	20.8

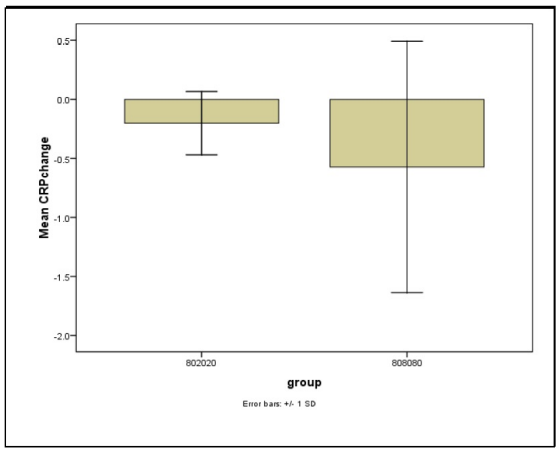

Figure 1. Mean of CRP change in both groups at three days atorvastatin therapy

In this study, no complications of treatment were reported and both methods of treatment were tolerated by patients.

Conclusion:

Plasma CRP level is elevated in the first days of ACS. It is due to systemic inflammatory response and have been associated with short and long term poor prognosis (6).

This study showed that both methods (low and high dose Atorvastatin) have significant effect on decreasing hs-CRP level in short term but reduction in high dose method was greater (-39.5% vs -31.2%, P=0.0185). Although means of hs-CRP level after 3 days treatment was not significantly different between groups.

Other studies have been shown dose dependent effect of atorvastatin on reduction of hs-CRP level (5,7). Most studies evaluated atorvastatin administration effectiveness during several weeks to several months (13,15) but the effect of short term (several days) less investigated.

Nesar Hossein et al studied 20, 40 and 60 mg atorvastatin effect for 6 months. They showed reduction of plasma level of hs-CRP in most patients but significantly reduction in 80 mg group incident after 3 months treatment and after 6 months for other dosages (7). However our study showed significantly reduction of plasma level of hs-CRP in both groups (80.80.80 mg and 80.20.20 mg) only after 3 days treatment.

Lower dose compare with 80 mg and 10 mg (add with 10 mg Ezctimibe) atorvastatin also showed significantly reduction in hs-CRP versus per-treatment after 8 weeks but did not significantly differ between two groups at pre-treatment and post-treatment (20). These findings were demonstrated in our study but in recent study mean absolute change was significantly different between groups. Walter et al demonstrated significantly effect of 30mg atorvastatin in hs-CRP concentration after 8 weeks (21).

Different doses at different duration of treatment have different effect. In recent study, 39.5% reduction is happened with 80mg per day atorvastatin after 3 days. However in Macin study, 62% reduction had been occurred with 40 mg per day atorvastatin at discharge (3±4 days) (6). High and aggressive dosages of atorvastatin (e.g. 80 mg) have similar effects in reduction of hs-CRP concentration (almost between 30% to 40%) (Table 3).

Therefore, administer of 80 mg atorvastatin is more effective than mild and moderate doses (1) Also, in recent study both methods therapy decrease hs-CRP between 30% to 40%. Our findings is near to results from a study done in an Iranian population (22).

In study of keles et al, comparing the effects of standard once daily 20 mg atorvastatin treatment with 20 mg administered every other day showed both methods have similar effects after one and three months treatment (17).

Meta analysis of PanPan proposed that difference effect may be due to a dosage effect rather than different statins (13).

Tousoulis et al showed that, statins required more than 1 week to significantly modify inflammatory response (15) findings of recent study and others studies display that statin effect is dependent to dosage, treatment duration and loading dose.

This study included only a limited number of patients from a single center and we have no data about clinical end-points because of short term follow-up period

Our findings showed that treatment with 80 mg atorvastatin for three days and and 80 mg for first day continued by 20 mg for next two days resulted in decreasing hs-CRP level in short term but the the

effect is more prominent in high dose group. We propose to use 80, 20 and 20mg dose for short term.

References:

1. Gensini GF, Gori AM, Dilaghi B, Rostagno C, Gaw A, Blanco-Colio LM, de Teresa E, Egido J, Farsang C, Leiter LA, Martineau P, Nozza A, Langer A. Effect of atorvastatin on circulating hsCRP concentrations: A sub-study of the Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration (ACTFAST) study. Int J Cardiol. 2010;142(3):257-264.
2. Jian-Jun Li, Ying Wang, Shao-Ping Nie, Chao-Yang Zhang,Yi-Shi Li, Ru-Tai Hui, Xin Zhen. Reduction of C-reactive protein by a single 80 mg of simvastatin in patients with unstable angina. Clin Chim Acta. 2007;376(1-2):163-167.
3. Shishehbor M, Patel T, Bhatt D, Using statins to treat inflammation in acute coronary syndromes: Are we there yet? Cleve Clin J Med. 2006;73(8):760-766.
4. Kinlay S, Schwartz GG, Olsson AG, Rifai N, Leslie SJ, Sasiela WJ, Szarek M, Libby P, Ganz P. High-dose atorvastatin enhances the decline in inflammatory markers in patients with acute coronary syndromes in the MIRACL study. Circulation. 2003;108(13):1560-1566.
5. Bonnet J, McPherson R, Tedgui A, Simoneau D, Nozza A, Martineau P, Davignon J. Comparative Effects of lO-mg versus 80-mg Atorvastatin on High-Sensitivity C-Reactive Protein in Patients with Stable Coronary Artery Disease: Results of the CAP (Comparative Atorvastatin Pleiotropic Effects) Study. Clin Ther. 2008;30(12):2298-2313.
6. Macin S, Perna E, Farı´as E, Franciosi V, Cialzeta J, Brizuela M, et al. Atorvastatin has an important acute anti-inflammatory effect in patients with acute coronary syndrome:Results of a randomized, double-blind,placebo-controlled study. Am Heart J. 2005;149(3):451-457.
7. Nesar Hossein V, Yosef Nejad K, Abdollahian F. Short-Term Therapy with High Dose Atorvastatin in Patients with Coronary Artery Disease Can Reduce Inflammatory Process. Acta Med Iran. 2010;48(4):218-221.
8. Wilson A, Ryan M, Boyle A. The novel role of C-reactive protein in cardiovascular disease: Risk marker or pathogen. Int J Cardiol. 2006;106(3):291-297.
9. Devaraj S, Singh U, Jialal I. The Evolving Role of C-Reactive Protein in Atherothrombosis. Clin Chem. 2009;55(2):229-238.
10. Zebrack J, Anderson J. Role of inflammation in cardiovascular disease: How to use C-reactive protein in clinical practice. Prog Cardiovasc Nurs. 2002;17(4):174-185.
11. Ridker P, Bassuk, Toth P. C-Reactive Protein and Risk of Cardiovascular Disease: Evidence and Clinical Application. Curr Atheroscler Rep. 2003;5(5):341-349.
12. Horn C, Ilg R, Sander K, Bickel H, Briesenick C, Hemmer B, Poppert H, Sander D. High-sensitivity C-reactive protein at different stages of atherosclerosis: results of the INVADE study. J Neurol. 2009;256(5):783-791.
13. PanPan H, YuGuo C, XingLi W, Feng X, JiaLi W, Yun Z. A meta-analysis of the effects of statins on serum C-reactive protein in Chinese population with coronary heart disease or hyperlipidemia. Chinese Science Bulletin. 2009;54(23):4404-4410.
14. Devaraj S, Rogers J, Jialal I. Statins and biomarkers of inflammation. Current Atherosclerosis Reports. 2007;9(1):33-41.
15. Tousoulis D, Antoniades C, Katsi V, Bosinakou E, Kotsopoulou M, Tsioufis C, et al. The impact of early administration of low-dose atorvastatin treatment on inflammatory process, in patients with unstable angina and low cholesterol level. International Journal of Cardiology. 2006;109(1):48-52.
16. Karaca I, Erdogan Ilkay E, Akbulut M, Yavuzkir M, Pekdemir M, Akbulut H, et al. Atorvastatin affects C-reactive protein levels in patients with coronary artery disease, Current Medical Research and Opinion. 2003;19(3):187-191.
17. Telat Keles T, Bayram N, KayhanT, Canbay A, fiahin D, Durmaz T, et al. The comparison

of the effects of standard 20 mg atorvastatin daily and 20 mg atorvastatin every other day on serum LDL-cholesterol and high sensitive C-reactive protein levels. Anadolu Kardiyol Derg. 2008;8(6):407-412.

18. Cheng Ding, Miao Hu, Yong-Jian Wu and Brian Tomlinson. Achievement of specified lipid and highsensitivity C-reactive protein levels with two statins in Chinese patients with Hypercholesterolaemia. Lipids in Health and Disease. 2015;14:107.
19. Paul M. Ridker. High-Sensitivity C-Reactive ProteinPotential Adjunct for Global Risk Assessment in the Primary Prevention of Cardiovascular Disease. Circulation. 2001;103:1813-1818.
20. Ostad MA, Eggeling S, Tschentscher P, Schwedhelm E, Böger R, Wenzel P, et al. Flow-mediated dilation in patients with coronary artery disease is enhanced by high dose atorvastatin compared to combined low dose atorvastatin and ezetimibe: Results of the CEZAR study. Atherosclerosis. 2009;205(1):227-232.
21. Walter T, Szabo S, Suselbeck T, Borggrefe M,Lang S, Swoboda S, et al. Effect of Atorvastatin on Haemostasis, Fibrinolysis and Inflammation in Normocholesterolaemic Patients with Coronary Artery Disease. Clin Drug Investig. 2010;30(7):453-460.
22. Zamani B, Babapour B, Doustkami H, Mousavi M. Compare the effect of high and low doses of atorvastatin on the levels ofhigh-sensitivity C-reactive protein in patients with acute coronary syndrome. Int J Res Med Sci. 2016;4(9).