Original Research Paper

Volume -10 | Issue - 5 | May - 2020 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Cardiology

SHORT AND LONG TERM SAFETY AND EFFICACY OF HIGH DOSE ATORVASTATIN IN REDUCING THE LEVEL OF hsCRP AND MAJOR ADVERSE CARDIAC EVENTS IN A GROUP OF PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION IN EASTERN INDIA.

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ABSTRACT **BACKGROUND :** Atherosclerosis is an inflammatory process and C reactive protein is an important biomarker of inflammation used clinically. Short term benefit of high dose loading Atorvastatin during periprocedural period in percutaneous coronary intervention{PCI} has been demonstrated in earlier studies. With this background the present study was designed to evaluate the short and longterm efficacy of high dose Atorvastatin in patients undergoing PCI in a tertiary care hospital in eastern India. **MATERIALS AND METHODS** This study was undertaken in the Department of Cardiology, SCB Medical College, Cuttack between September 2013 to August 2015. All patients undergoing PCI between September 2013 to August 2015 were included in the study. Patients with CKD and CLD and known allergic reaction to statins were excluded from the Study. Patients who developed drug induced liver injury, myalgia and myopathy were also excluded.All patients were followed up for one year. Patients in the Study arm received Atorvastatin 80 mg from the day of procedure, independent of baseline lipid levels, starting before the procedure i.e. immediately after hospitalization and continuing till one month after the procedure with the same dose and then reducing the dose to 40 mg for next 11 months. The patients in control arm received Atorvastatin 20 mg from the day of procedure and continued for 1 year. **RESULTS:** There were 104 patients in study group and 102 patients in control group. The demographic characteristics of the 2 treatment groups at baseline were similar. All 206 patients were followed up to 1 yr. The hs CRP level surged in day one and came down in both groups by day 7. It was significantly low in study group on day 7 and through out the study period. 2 patients of the 80 mg group & 12 patients of 20 mg group admitted within 1 yr period due to unstable angina/acute coronary syndrome. **CONCLUSION** High dose atorvastatin 80 mg in peri-PCI period reduce the hsCRP level and MACE significantly, is very well tolerated in Indian population irrespective of age, sex, bodyweight, co morbid conditions.

KEYWORDS :

INTRODUCTION

Atherosclerosis is an inflammatory response to injury was first described by Virchow in mid 19th century. According to that concept, endothelial denudation led to platelet aggregation and release of platelet-derived growth factors. These growth factors trigger the proliferation of smooth muscle cells in the arterial intima and that form the nidus of the atherosclerotic plaque.[1]

For a variety of reasons, CRP has emerged as a leading biomarker of inflammation for clinical application.

CRP has considerable chemical stability, requires no special precautions for sampling, and has a relatively long half-life without the diurnal variation that plagues certain other biomarkers.2,3

More than a dozen large-scale prospective cohort studies indicate that hsCRP predicts incident myocardial infarction, stroke, and cardiovascular death even after full adjustment for the traditional Framingham covariates4.

Percutaneous coronary angioplasty is an invasive procedure where the stenosed major coronary arteries were dilated with stents mounted over balloon at high atmospheric pressure. It invokes injury to vessel walls. Inflammatory responses and platelet activation following injury are considered to be the primary causes of inverse events after coronary angioplasty 5.

In stable clinical situations, it is thought that statins mediate their primary cardiac benefit via low-density lipoprotein reduction and plaque stabilization. However, in acute situations (such as acute coronary syndromes or coronary interventions). It also acts in a variety of ways to counter the inflammatory response[6].

The proposed present study of periprocedural high dose statins to prevent cardiac complications is a derived from several previous studies. In 2002, Herrmann et al. found that patients who received statins 7 days before PCIs had a lower incidence of MI compared with statin nonusers.[7]

The ARMYDA (Atorvastatin for Reduction of Myocardial Damage During Angiolasty) trial was the first randomized, prospective study to test whether statin treatment decreased myocardial injury and improved outcomes after coronary angioplasty.[8]

The ARMYDA-ACS (Atorvastatin for Reduction of Myocardial Damage During Angioplasty-Acute Coronary Syndromes) trial studied this effect in those with unstable coronary syndromes, finding that 80 mg atorvastatin given 12 h before coronary angioplasty decreased the primary composite outcome of death, MI, or revascularization (5% vs. 17%, p=0.01).9

Among those on longterm statin treatment undergoing PCI for stable angina, the ARMYDA-RECAPTURE study found that acute atorvastatin loading (80 mg 12 h before PCI) reduced the 30 day incidence of cardiac events from 9.4% to 3.7% (p=0.037), principlally due to a reduction in MI.[10]

In statin naïve patients, the Italian NAPLES (Novel Approaches for Preventing or Limiting Events) II trial demonstrated that a single pre-procedural 80 mg loading dose of atorvastatin significantly decreased periprocedural MI (9.5% vs. 15.8%, p=0.014).[21]

However, all these studies tried to show only short term benefits from high dose of atorvastatin during peri-PCI period.[8,9,10,11]

The present study is designed to evaluate the long term effects of high dose of atorvastatin 80 mg loading before the PCI on the rise of inflammatory biomarker hs-CRP and MACE.

With this background the present study was undertaken to study the efficacy of high dose Atorvastatin in reducing hsCRP and Major Adverse Cardiac Events(MACE) in patients undergoing Percutaneous Coronary Intervention(PCI) in a tertiary care hospital in Eastern India.

OBJECTIVE OF THIS STUDY

To evaluate the efficacy of Atorvastatin to reduce the hs-CRP level and reduction of major adverse cardiac events (MACE) in a group of patients undergoing PCI procedure in eastern India.

MATERIALS AND METHODS

This study was undertaken in the Department of Cardiology, SCB Medical College, Cuttack between September 2013 to August 2015.

Inclusion Criteria: All patients undergoing PCI between September 2013 to August 2015 were included in the study.

Exclusion Criteria: Patients with CKD and CLD and known allergic reaction to statins were excluded from the Study. Patients who developed drug induced liver injury, myalgia and myopathy were also excluded.

Follow up: All patient were followed up for one year.

Study Method(designed / protocol):

This is a prospective randomized controlled Study. Institutional ethics committee approval was taken prior to enrollment of patients. Informed consent was obtained from study participants. Detail history taking and physical examination was done and recorded in proper format. Standard investigations were done before PCI and patients were randomly allocated to two groups: study and control.

In this prospective randomized control trial, patients in the Study arm received Atorvastatin 80 mg from the day of procedure, independent of baseline lipid levels, starting before the procedure i.e. immediately after hospitalization and continuing till one month after the procedure with the same dose and then reducing the dose to 40 mg for next 11 months. The patients in control arm received Atorvastatin 20 mg from the day of procedure and continued for 1 year. Those who were receiving other statins before hand switched to Atorvastatin either in the study arm or in the control arm. Those who were receiving statin at dose equivalent of Atorvastatinmore than 20 mg were included in the study arm. Cases were followed up at 1month, 3month, 6month and 1year.

Their hs-CRP levels was measured just before the procedure, after 24 hours, after 7 days, after 1 month and after 1 year of the procedure. Lipid profile was measured at 1month, 3month, 6month and 1year.

Major adverse cardiac events (MACE) was defined as death, target vessel revascularization, unplanned hospitalization due to acute coronary syndrome. All MACE in 1year were recorded and analysed.

RESULTS:

The demographic characteristics of the 2 treatment groups at baseline were similar.

All 206 patients were followed up to 1 yr.

2 patient of the 80 mg group & 12 patients of 20 mg group admitted within 1 yr period due to unstable angina/acute coronary syndrome.

Parameter	Study (n=104)	Control (n=102)	p-value
Age (yr)	55.02±9.315	55.28±10.316	0.7
Male	84(88%)	82(80%)	0.95
Diabetes	26(25%)	26(25%)	0.594
Hypertension	60(57%)	60(58%)	0.902
Smoker	48(46%)	48(47%)	0.927
+ve family h/o	34(32%)	34(33%)	0.52
LDL Day 0	113.92±10.13	114.38±10.178	0.3
LDL 1 month	109.80±10.91	110.36±10.652	0.45
LDL 1 year	83.0±4.986	100.44±7.611	<0.001
HDL	36.24±5.041	35.88±44.796	0.7
TG	197.0±46.522	196.88±44.796	0.2
TCL	224.48±44.841	226.16±43.499	0.22
ALT day 0	39.12±8.861	39.10±9.134	0.23
ALT 1 month	32.10±5.994	33.26±6.586	0.2
ALT 1 year	26.94±3.706	27.28±3.949	0.2
hsCRP day 0	8.96±6.01	8.75±6.05	0.5
hsCRP day 1	15.652±10.13	16.064±9.19	0.4
hsCRP day 7	4.86±2.13	8.38±4.16	<0.05
hsCRP 1 month	2.76±0.638	4.026±1.127	<0.001
hsCRP 1 year	1.96±0.437	3.374±0.564	<0.001

Main Demographic/Clinical Features in the study & control Groups

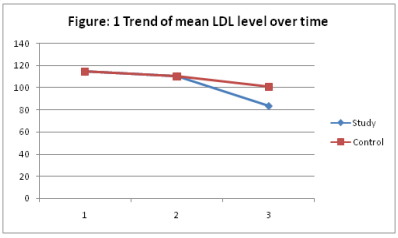
Parameters shown as number of patient % or mean±SD

LDL-low density lipoprotein, HDL-high density lipoprotein, TG-triglyceride, TCL-total cholesterol, ALT-alanine transaminase (SGPT), hsCRP-high sensitive C-reactive protein

In this study most patients who underwent angioplasty was having presentation with STEMI.

As STEMI patients admitted more in our Institution so their representation has also become highest in this study.The create registry showed that among patients presenting with acute coronary syndrome, 60.6% had STEMI.

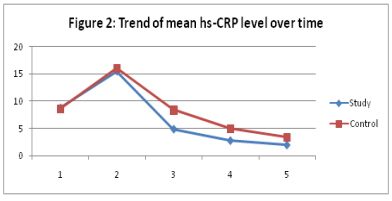
This study supports the similar trend that found in eastern Indian population.



1 = LDL on day 0

2 – LDL on 1 month

3 = LDL on 1 year. On admission mean LDL level in our study & control population was normal. Mean LDL level has a trend of declining after 1 month of atrovastatin use.This phenomenon became highly significant (p=<0.001) in the study arm.



hsCRP day 0	8.966.01	8.756.05	0.5
hsCRP day 1	15.65210.13	16.0649.19	0.4
hsCRP day 7	4.862.13	8.384.16	<0.05
hsCRP 1 month	2.760.638	4.0261.127	<0.001
hsCRP 1 year	1.960.437	3.3740.564	<0.001

1 = hsCRP on day 0, 2 = hsCRp on day 1, 3 = hsCRP on day 7,
4 = hsCRP on 1 month, 5 = hsCRP on 1 year

hsCRP surged in the 1st day after the procedure in both the groups which was highly significant. After 1 day the level of the marker showed declining trend in both the arm. However the rate of declining was more in the study arm than the control.

hsCRP level came below the baseline at 7 days & became nearly low risk category at 1 yr period in the study arm despite underlying atherosclerotic heart disease.The level of hsCRP showed highly significant difference between study &control group after day 1 of the procedure & the difference gradually became more prominent over time.

Analysis of the reports

Mean age in the control (20 mg atrovastatin) group was 55.2810.316 & in the study (80mg) group was 54.899.283.

Maximum patients belonged to age group of 41-60 yrs of age (59.6% in the study, & 56.8% in the control), least representative group was <40 yrs.

23.1% of patient from study group & 22.5% of from control group were diabetic. Mean FBS value was 109.6832.619 for control & 107.9625.894 for the study group.

In the study group 57.7% were hypertensive & 58.1% had hypertension in control group.

32.6% & 33.3% respectively from study & control were having positive family history suggestive of premature CAD.

Patients who smoked or use any other forms of tobacco were 32.6% & 33.3% respectively from study & control group.

On admission baseline LDL were 114.3810.178 for control population & 113.9210.131 in the study population. After 1 year of treatment significant LDL level was decreased in the study population up to around 83.004.986 mg where in control population it was 100.447.611

mg, though this difference was not obvious in 1 month where mean values were 109.8010.915 & 110.3610.652 mg respectively.

Mean ALT (SGPT) values didn't change much in 1 month (32.105.994 vs. 33.266.586) or 1 year period (26.943.706 vs. 27.283.949).

Significant reduction of hsCRP levels were observed in 1 day between study &control group (15.65200010.136602 vs. 16.0640009.1999503), 1 month (2.7680000.6386977 vs.4.9260001.7274270), 1 year (1.9660000.4378099 vs. 3.3740000.564533). Mean hsCRP level in the study arm was 1.96 mg/l & 3.37 mg/l in the control arm.

MACE (major adverse cardiac events) in the form of repeat unplanned hospitalization occured in 2 patient of study population (1.9%) & 12 patients (11.76%) in control population.

So absolute risk reduction = a – b = 11.76 – 1.92 = 9.84% and Relative risk reduction = a- b / b = 83.76%.

It occurred between 4 – 11 months of the initiation of study (earliest at 4.2 month & latest at 10.5 months).

Patients mainly presented with acute coronary syndrome. 9 patients of control group and one patient in study group had elevated Trop-I level. All patients were hospitalized & check angiogram was performed.

8 patients showed marginal lumen loss within the stent region (7 from control and 1 from study group), other patients had patent stent & without any lesion in same or other vessels.

All patients of control group study population having MACE had hsCRP value 2 & 2.2 mg respectively at 1 yr & 1 month period.

From our observation it is evident that MACE occurred frequently to those patients in control population whose hsCRP levels remained at higher level in comparison to other patients in the case group.

In our study all patients received optimal medical management including dual antiplatelets, b-blockers & ACE-inhibitors or ARBs.

Regarding compliance to Atorvastatin, all patients showed excellent compliance. Only 6 patients of initial 107 patients (2.8%) developed elevation of liver enzymes that with 7 days of initiation.

Other patients tolerated 80mg Atorvastatin excellently.

2 patients, out of initial 214 patients, complained about myalgia (0.09%) for which dose was reduced.

Gastrointestinal disturbances mainly like fullness of abdomen and burning sensation were noticed and treated symptomatically.

DISCUSSION

This study indicates that pretreatment with Atorvastatin loading (80mg) before percutaneous coronary intervention (PCI) and continuation of same high dose for at least 1 month & later 40mg for at least up to 1 year period improves outcome irrespective of baseline LDL levels.

In particular our regimen was associated with 9.84% absolute risk reduction of major adverse cardiac events (MACE) at 1 year period & 83.76% relative risk reduction in the same duration.

In our study population 25.7% of patients who presented with stable angina were on statin therapy but 74.3% of patients who presented with acute coronary syndromes (ACS) were statin naïve.

The long term benefit was essentially driven by significant reduction of inflammation as depicted by deceasing hsCRP values.

Similar studies like the original ARMYDA8 and in the ARMYDA ACS9 trials only statin-naïve patients were enrolled but. The ARMYDA-RECAPTURE trial10 included patients who were on statins before hand.

In original ARMYDA study8, patients with chronic stable angina were randomized to receive 7 day pre-treatment before PCI with atrovastatin 40 mg/day or placebo, and a significant 81% risk reduction of periprocedural MI was observed in the statin arm.

The ARMYDA-ACStrial9 enrolled patients with unstable angina or non-ST-segment elevation ACS, in whom 80 mg of atrovastatin administration led to 88% risk reduction of cardiac events at 1 month versus placebo, as well as to a 3 fold reduction of per-procedural MI.

In the ARMYDA-RECAPTURE trial10 an acute bolus of 80mg atorvastatin given 12 h before intervention followed by a further 40 mg pre-procedural dose was associated with 50% relative risk reduction of MACE at 30 days versus placebo.

All these trials with similar study designs showed short term benefits from high dose of atorvastatin.

In this study, we have followed patients upto 1 yr. after the procedure. It has shown that use of high dose atorvastatin during the per-procedure period of PCI resulted in significant reduction of hsCRP & MACE in comparison to low dose in the longterm (1 yr).

Possible mechanisms of atorvastatin cardio protection during the PCI might be reduction of intercellular cell adhesion molecule-1 and E-selectin levels as suggested from ARMYDA-CAMs (Atorvastatin for Reduction of Myocardial Damage during Angiolasty-Cell Adhesion Molecules) study.12

Other explanations include

a. Atorvastatin induced early increase of endothelial progenitors cells differentiation and subsequent augmentation of circulating endothelial progenitors cells, with attendant cardioprotective effects 12.
b. Vasodilatation of coronary micro vessels,
c. Direct antithrombotic effect and
d. Possible direct protective effect on myocardial cells.13

independent reduction of LDL level leading to reduction of adverse events in CAD patients require long continuationaround 2 years of statins therapy24. But in this study we have observed significant reduction of cardiac events between 2 groups within 1 yr time.

So it is unlikely that the benefit shown in this study is due to lipid lowering. On the contrary it proves the strong pleotropic effects of statin that can be useful in peri-PCI period.

As all the patients in this study received guideline directed optimal medical therapy before and after the procedure, it is less possible for these drugs to acquire benefits of MACE only in 80 mg arm.

So it is obvious that pleotropic effects of statin are neutral with other cardioprotective drugs but only related with the dose of the statins.

It is difficult to answer the probable cause of angina in that patient of 80 mg groups who developed MACE.

As the coronary angiography was normal regarding the patency of stents & no new lesion or increment of preexisting lesions was found, probably the cause might be microvascular.

In the other side of control group where 12 patients developed MACE, 8 patients developed minor degree (20-40%) of late lumen loss within the stent without new lesion & 4 patients had patent stents with no new lesion or increment of preexisting lesions.

So it is likely that in the control group on 20 mg statin, the dose was not adequate to halt the inflammatory milieu in the peri-stent region as well as associated microvascular cause can't be ruled out.

Regarding the tolerance to such high dose of atorvastatin (80mg), minor gastrointenstional side effects were noticed & successfully managed with symptomatic treatments.

In this study the basic demography of the population like participation by gender, age distribution, smoking habit, presence of diabetes, diagnosis at presentation nearly matched with the similar findings of Create registry on Indian population except the finding of presence of hypertension which was higher in this study.

It might be possible that the create registry included only data of ACS patients & this study included both ACS & stable angina patients which has made this difference.

CONCLUSION

The present study shows high dose atorvastatin 80 mg before percutaneous coronary intervention (PCI) and its continuation can reduce major adverse cardiac events at 1 year.

The 80mg atorvastatin is very well tolerated in Indian population irrespective of age, sex, bodyweight, co morbid conditions.

Probably this is the first study of such high dose of atorvastatin on Indian population simultaneously showing good tolerance as well as its excellent dose related pleotropic effects.

If this findings can be confirmed through a big randomized trial, it may support the routine use of high dose atorvastatin 80 mg in peri-PCI period and its continuation to prevent the MACE.

As incidence of atherosclerotic heart disease is increasing day by day & coronary angioplasty is being performed more frequently, this important observation would help to improve the overall outcome as well as decrease the cost burden.

LIMITATIONS OF THE STUDY

1. Sample size was relatively small (206 patients) in relation to large number of patients suffering from coronary artery disease.
2. It is a single center study limited to a hospital that can limit the outcome showing biases.
3. Economic constraints and feasibility was a major limiting factor in angioplasty and its follow up with specialize.

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