Original Article

To study the effect of high dose Atorvastatin 40 mg versus 80 mg in patients with dyslipidemia

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A R T I C L E   I N F O

A B S T R A C T

Objective: Primary objective was to compare the effects of atorvastatin 40 mg vs 80 mg on LDL-C in Indian patients with atherosclerotic dyslipidemia. Secondary objectives were to compare the effects of atorvastatin 40 mg vs 80 mg on HDL-C and triglycerides and also comparing of side effects (myopathy, hepatotoxicity and new onset diabetes mellitus) of both doses.

Method: This Study is A Prospective, randomized, open-label, comparative study. This study was conducted on 240 patients of dyslipidemia (as per ACC/AHA 2013 lipid guidelines) attending the OPD/wards/CCU of department of cardiology, Sir Ganga Ram Hospital. They were randomly divided into 2 groups of 120 each. Group A consisted patients who received Atorvastatin 40 mg daily and Group B Atorvastatin 80 mg daily. The follow up period was 6 months.

Results: At 3 and 6 month follow up, Atorvastatin 40 mg leads to mean LDL cholesterol reduction of 47.18 ± 20.81 & 50.03 ± 18.06 respectively. While Atorvastatin 80 mg results in LDL reduction as 50.11 ± 15.85 & 52.30 ± 13.72. The comparison between two doses revealed a non-significant difference (p = .118 & p = .149 respectively).

At 6 months of follow up, few patients reported myalgia (2 in group A and 7 in Group B). The difference between groups was significant (p = .045). Although none of our patient had significant elevation of CPK.

Conclusion: This study concluded that both doses of atorvastatin (40 & 80 mg) are equally efficacious in improving dyslipidemia but higher dose leads to more incidence of myalgia.

What is already known?

High dose statins (40mg and 80 mg atorvastatin) are important in reducing ASCVD events. However, these high statin doses are associated with increased adverse effects like liver enzyme elevation, new onset diabetes mellitus and myalgia/myopathy which are related to dose.

What this study adds?

40 mg dose of atorvastatin is as effective as 80 mg atorvastatin for obtaining guidelines directed lipids level in Indian patients of dyslipidemia. Besides this by reducing statin dose from 80 mg to 40 mg some dose related adverse effects of statins like myalgia can be decreased.

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1. Introduction

Dyslipidemia management is always a challenge in clinical practice. Dyslipidemia prevalence is continuously increasing in Indians, even in younger age groups. Besides this dyslipidemia pattern is quite different from Western countries.[1] Dyslipidemia is an important modifiable cardiovascular risk factor.[2,3] Asian populations have a distinct pattern of dyslipidemia which includes- Increased triglycerides, lower HDL cholesterol and increased level of small dense LDL cholesterol.[4]

Statins have an important role in management of high risk patients of ASCVD (atherosclerotic cardiovascular disease). High intensity statin therapy (which lowers LDL cholesterol by ≥50%) is a critical factor in reducing ASCVD events. Unfortunately high doses of statins sometime leads to increased adverse effects like elevated liver enzymes, new onset diabetes mellitus and myalgia/myopathy which are dose related.[5–10]

The ACC/AHA 2013 Lipid guideline have given two different doses in the definition of high intensity statins. As per guideline it was 40–80 mg for atorvastatin, while 20–40 mg for rosuvastatin.[11]

Our study is probably second only study in India which is comparing 40 mg and 80 mg doses of atorvastatin. Hypothesis of our study was that 40 mg dose of atorvastatin is as effective as 80 mg atorvastatin to reach recommended goals in Indian patients of dyslipidemia. Besides this by reducing statin dose from 80 mg to 40 mg dose related adverse effects of statins will be decreased.

2. Methods

Patients admitted in Dharma Vira Heart Center, Sir Ganga Ram Hospital, New Delhi with atherosclerotic cardiovascular disease were enrolled for the study.

2.1. Study design

It was a randomized open study. This study was conducted on 240 patients of dyslipidemia (as per ACC/AHA 2013 lipid guidelines) attending the OPD/wards/CCU of department of cardiology, Sir Ganga Ram Hospital.

2.2. Sample size calculation

A previous study indicated a similar protocol showed that the LDL-C at day 44 was 66.61 with SD 21.25 in Group A whereas in Group B it was 59.44 with SD 18.14. Sample size of 120 patients per group was calculated based on a mean difference of 7.17 in LDL-C (primary end point) between the two groups, at two-sided alpha of 0.05, and a power of 80%.

2.3. Inclusion criteria

Any Indian patient >18 years of age with dyslipidemia (LDL-C ≥100 mg/dl) and atherosclerotic cardiovascular disease willing to participate in trial.

2.4. Exclusion criteria

1) Patient already on treatment with any dose of any statin.
2) Abnormally elevated liver enzymes (ALT and/or AST more than 2 times ULN).
3) Elevated creatine phosphokinase (CPK) (more than 3 times ULN).
4) Patient is already a diagnosed case of diabetes.
5) Patient is a known case of advanced liver/kidney disease or malignancy.
6) Patients is a taking any drug which are strong inhibitors of CYP3A4 enzymes like macrolide antibiotics (such as erythromycin, roxithromycin etc.), azole antifungals (ketoconazole, fluconazole etc.), cyclosporine, gemfibrozil etc.
7) Pregnant and/or lactating women.

2.5. Statistical methods

The quantitative variables were expressed as mean ± sd and compared between groups using unpaired *t*-test/Mann-Whitney test and within groups using paired *t*-test/Wicoxon test. The qualitative variables were expressed as frequencies/percentages and compared between groups using Chi-square/Fisher's exact test. A p-value < 0.05 was considered statistically significant. SPSS version 16.0 software was used for statistical analysis.

3. Results

A total of 240 patients of Dyslipidemia were included in study. These patients were randomly divided into 2 groups of 120 each, group A and group B.

The age distribution of study population lies between 20 and 90 years. Age of the patients was comparable between the two groups and statistically not significant (p = .128). Majority of the patients in both the groups are male. Difference between both groups in sex distribution was statistically insignificant (p = .111) (Table 1).

In group A 06 and 04 patients were lost to follow up at 3 and 6 months respectively. Similarly, in group B 08 and 03 patients were lost to follow up at 3 and 6 months respectively (Fig. 1).

Patient were followed up after 3 and 6 months for change in LDL-Cholesterol, HDL-Cholesterol, triglycerides, glycated hemoglobin (HbA1c), CPK, SGOT, SGPT and muscle symptoms (Table 2).

Both groups were evaluated for any muscle symptoms during follow up period. In group A, only 2 patients while in group B, 7 patients complained of myalgia after starting of treatment (Table 3).

In terms of subjective symptoms of myalgia, difference between two groups was statistically significant (p = .045) (Table 4).

4. Discussion

It is a known fact that high dose of statin treatment (Atorvastatin 40 or 80 mg) reduces LDL cholesterol by ≥50% of their baseline value. Same was confirmed in our study. In term of

Table 1
Age and sex distribution of patients.

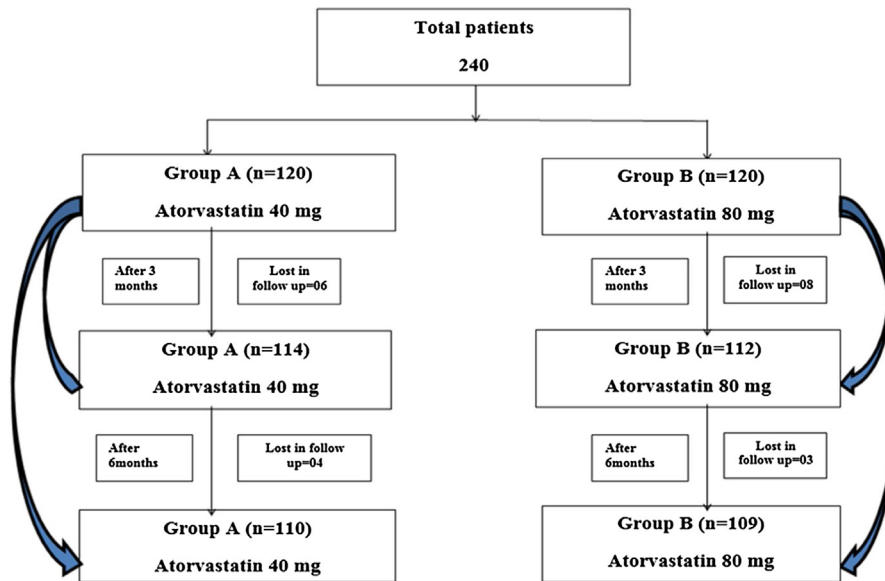|	40 mg		80 mg	
	n	%	n	%
Age (years)				
20–30	3	2.50%	0	0.00%
30–40	4	3.33%	5	4.17%
40–50	19	15.83%	13	10.83%
50–60	38	31.67%	44	36.67%
60–70	41	34.17%	40	33.33%
70–80	13	10.83%	14	11.67%
80–90	2	1.67%	4	3.33%
TOTAL	**120**	**100%**	**120**	**100%**
mean ± sd	57.48 ± 11.17		59.05 ± 10.25	
p-value	**0.128**			
Gender				
Male	88	73.33%	96	80.00%
Female	32	26.67%	24	20.00%
TOTAL	**120**	**100%**	**120**	**100%**
p-value	**0.111**			

Fig. 1. Randomization and follow up.

Table 2
Efficacy of both doses of statin on follow up.

Groups	LDL Cholesterol			% decrease in LDL Cholesterol	
	Baseline	3 months	6 months	At 3 months	At 6 months
40 mg Group	136.72 ± 22.57	70.25 ± 25.63	66.53 ± 21.1	47.18 ± 20.81	50.03 ± 18.06
80 mg Group	136.43 ± 18.81	67.07 ± 20.69	64.18 ± 17.58	50.11 ± 15.85	52.30 ± 13.72
p-value (40 mg vs 80 mg)	0.457	0.153	0.187	0.118	0.149

Groups	HDL Cholesterol			% increase in HDL Cholesterol	
	Baseline	3 months	6 months	At 3 months	At 6 months
40 mg Group	36.95 ± 7.2	38.81 ± 6.78	39.45 ± 7.07	9.52 ± 30.07	11.36 ± 28.62
80 mg Group	38.48 ± 7.25	39.91 ± 7.02	40.20 ± 6.85	7.74 ± 26.43	9.02 ± 27.47
p-value (40 mg vs 80 mg)	0.052	0.115	0.211	0.319	0.269

Groups	Triglycerides			% decrease in triglycerides	
	Baseline	3 months	6 months	At 3 months	At 6 months
40 mg Group	121.31 ± 30.45	94.39 ± 22.05	90.70 ± 20.4	20.60 ± 17.27	24.11 ± 16.41
80 mg Group	114.13 ± 38.79	83.10 ± 24.21	79.34 ± 20.39	22.29 ± 24.5	26.15 ± 21.3
p-value (40 mg vs 80 mg)	0.056	<0.001	<0.001	0.274	0.214

percentage decrease in LDL-Cholesterol at 3 and 6 months difference between both groups was statistically insignificant ($p = .118$ & 0.149 respectively). It was consistent with a previous study done by Deedwania PC et al In their study 740 patients of the United States and Canada were treated with atorvastatin 10 mg or 20 mg doses and they found 40% and 47% decline in the level of serum LDL cholesterol with atorvastatin 10 mg and 20 mg respectively ($p = NS$).[12]

Our study was not consistent with CURE-ACS study done by Upendra kaul et al They found a dose-dependent response in reduction of LDL cholesterol with 12 weeks treatment of atorvastatin 80 mg versus 40 mg (27.5% vs. 19.04%) which was statistically significant.[13]

Reason for this inconsistency is not clear but it may be due to low baseline LDL cholesterol in CURE-ACS study. Baseline mean LDL-Cholesterol was 80.95 ± 26.19 mg/dl and 80.46 ± 24.87 which decreased to 65.54 ± 22.84 mg/dl and 58.33 ± 18.11 mg/dl in 40 mg versus 80 mg group respectively at the end of 86 days. In our study baseline mean LDL-Cholesterol was 136.72 ± 22.57 mg/dl and 136.43 ± 18.81 mg/dl in 40 mg versus 80 mg group respectively.

A meta-analysis of 32,258 patients of dyslipidemia was done by Philip J. Barter et al It included 37 randomized studies of different types of statin (Rosuvastatin, atorvastatin, and simvastatin etc.). Effect of these statins on HDL cholesterol level was assessed in this meta-analysis. They found that increase in serum HDL cholesterol was inversely related to dose of atorvastatin. There was 4.5% increase in serum HDL cholesterol with 10 mg dose while there was a 2.3% increase in serum HDL cholesterol with 80 mg dose of atorvastatin.[14] It was concordant with our study which showed percentage increase in HDL-Cholesterol in the range of 9.52 ± 30.07 and 11.36 ± 28.62 at 3 and 6 months follow up respectively in 40 mg group. While in 80 mg group, percentage increase in HDL-Cholesterol was 7.74 ± 26.43 and 9.02 ± 27.47 at 3 and 6 months follow up respectively.

In our study percentage decrease in triglyceride was 20.60 ± 17.27 and 24.11 ± 16.41 at 3 and 6 months follow up respectively in 40 mg group while it was 22.29 ± 24.5 and 26.15 ± 21.3 at 3 and 6 months follow up respectively in 80 mg group. These results are consistent with a previous study done by Jones PH et al They concluded that 6 weeks of treatment with

Table 3
Safety profile of both doses of statin on follow up.

Groups	HbA1C			% increase in HbA1C	
	Baseline	3 months	6 months	At 3 months	At 6 months
40 mg Group	5.19 ± 0.24	5.19 ± 0.23	5.21 ± 0.23	0.06 ± 5.85	0.38 ± 6.27
80 mg Group	5.17 ± 0.24	5.19 ± 0.25	5.20 ± 0.24	0.63 ± 6.74	0.74 ± 6.75
p-value (40 mg vs 80 mg)	0.243	0.454	0.292	0.247	0.340

Groups	CPK			% increase in CPK	
	Baseline	3 months	6 months	At 3 months	At 6 months
40 mg Group	76.98 ± 28.35	97.44 ± 31.75	97.79 ± 27.95	38.32 ± 62.84	37.56 ± 57.96
80 mg Group	75.56 ± 27.83	104.54 ± 35.32	103.50 ± 33.11	56.24 ± 78.03	53.17 ± 73.15
p-value (40 mg vs 80 mg)	0.347	0.056	0.085	0.029	0.041

Groups	SGOT			% increase in SGOT	
	Baseline	3 months	6 months	At 3 months	At 6 months
40 mg Group	30.09 ± 9.33	44.05 ± 14.88	45.54 ± 17.13	61.46 ± 73.58	65.73 ± 82.77
80 mg Group	31.00 ± 8.31	52.59 ± 23.81	53.87 ± 23.14	82.11 ± 99.4	86.14 ± 92.05
p-value (40 mg vs 80 mg)	0.213	<0.001	0.001	0.038	0.043

Groups	SGOT			% increase in SGOT	
	Baseline	3 months	6 months	At 3 months	At 6 months
40 mg Group	30.09 ± 9.33	44.05 ± 14.88	45.54 ± 17.13	61.46 ± 73.58	65.73 ± 82.77
80 mg Group	31.00 ± 8.31	52.59 ± 23.81	53.87 ± 23.14	82.11 ± 99.4	86.14 ± 92.05
p-value (40 mg vs 80 mg)	0.213	<0.001	0.001	0.038	0.043

Groups	SGPT			% increase in SGPT	
	Baseline	3 months	6 months	At 3 months	At 6 months
40 mg Group	33.53 ± 15.26	47.61 ± 19.84	48.84 ± 24.77	69.97 ± 94.46	75.15 ± 120.14
80 mg Group	30.51 ± 13.78	52.84 ± 24.04	54.72 ± 26.01	90.51 ± 88.03	100.85 ± 107.78
p-value (40 mg vs 80 mg)	0.055	0.038	0.044	0.046	0.049

Table 4
Myalgia during follow up.

Myalgia	40 mg		80 mg		p-value (40 mg vs 80 mg)
	n	%	n	%	
Yes	2	1.67%	7	5.83%	0.045
No	118	98.33%	113	94.17%	
TOTAL	120	100%	120	100%	

atorvastatin 40 and 80 mg decreases serum triglycerides by 26.8% and 28.2% respectively.[15]

A large population based study was published in 2013. In this study 4,71,250 diabetes naïve patients were treated with different doses of statin. Study concluded that moderate and high dose statins were associated with an increased risk of new onset diabetes as compared to low doses of statins.[16] Our results showed that baseline mean HbA1c was 5.19 ± 0.24% in 40 mg group, which increased to 5.19 ± 0.23% and 5.21 ± 0.23% at 3 and 6 months respectively. While in 80 mg group baseline mean HbA1c was 5.17 ± 0.24%, which increased to 5.19 ± 0.25% and 5.20 ± 0.24% at 3 and 6 months respectively. No patient in any group had HbA1c value more than upper limit of normal and No patient developed new onset diabetes. Our results are inconsistent with previous studies, which may be due to the fact that our study duration was very short as compared with previous studies.

Our results showed that, in terms of percentage increase in SGOT and SGPT at 3 and 6 months difference between both groups was statistically significant ($p < 0.05$). No patient in any group developed liver enzymes elevation >3 times ULN but higher dose leads to more elevation in liver enzymes as compared to lower dose of atorvastatin. These results are consistent with NASDAC study, which was performed for evaluation of safety and efficacy of different doses of atorvastatin (10, 20, 40, and 80 mg). There was persistent elevations in liver enzymes >3 times ULN in 0.4% and 0.9% of patients with 20 vs 80 mg doses of atorvastatin respectively in comparison to placebo.[17]

In our study myopathies was assessed by subjective complaint of myalgia and by measurement of Creatine phosphokinase (CPK) during 3 and 6 months follow up in both groups. There was statistically significant elevation in serum CPK in both groups but no patient had CPK level more than upper limit of normal. In term of percentage increase in CPK at 3 and 6 months difference between both groups was statistically significant ($p = .029$ & 0.041 respectively).

In 40 mg group, only 2 patients while in 80 mg group, 7 patients complained of myalgia after starting of treatment. In terms of subjective symptoms of myalgia, difference between two groups was statistically significant ($p = .045$). Our results are consistent with a previous study done by Beth A. Parker et al They studied 420 statin-naive patients who were treated with atorvastatin 80 mg or placebo. Clinical symptoms and CPK level were measured in both groups during 6 months follow up. They found that mean CPK level increased 20.8 ± 141.1 units per liter (P < 0.0001) by treatment with atorvastatin as compared to placebo but no individual CPK value was >10 time ULN. Myalgia developed in 19 patient receiving atorvastatin and 10 patients in placebo group (P = .05).[18]

5. Conclusion

This study concluded that 40 mg dose of atorvastatin is as effective as 80 mg atorvastatin for obtaining guidelines directed lipids level in Indian patients of dyslipidemia. Besides this by reducing statin dose from 80 mg to 40 mg some dose related adverse effects of statins like myalgia can be decreased but further long term follow up is needed for assessment of all adverse effects.

Acknowledgments

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