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Original Article

Comparison of Atorvastatin Alone and its Combination with Ezetimibe among Mixed Hyperlipidemic Patients

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Abstract

Background: Lowering the lipid levels remains the basis of recent medical therapy for preventing cardiovascular events. Statin treatment to attain target low-density lipoprotein cholesterol (LDL-C) levels is still associated with residual risk. ***Objective:*** To compare the efficacy of Atorvastatin and Atorvastatin combined with Ezetimibe among mixed hyperlipidemic patients. ***Methodology:*** This was a prospective interventional study among the 58 diagnosed mixed hyperlipidemic patients in the outpatient department (OPD) of the Department of Cardiology at the Sylhet MAG Osmani Medical College Hospital during February to November, 2023. Patients were divided into two groups. Group I had a combination of Atorvastatin 10mg and Ezetimibe 10mg, whereas Group II took Tab. Atorvastatin 20mg once daily at night for 12 weeks. ***Results:*** After 12 weeks of treatment, a comparison of lipid profile changes between the combination therapy group and the Atorvastatin group revealed a significant reduction ($p<0.05$) in total cholesterol (35.7% vs. 30.1%), triglycerides (30.6% vs. 16%), and LDL-C (47.5% vs. 40.1%). In the combination therapy group, ALT levels increased by 4.6%, compared to a 3.8% increase with Atorvastatin treatment alone. Combination therapy led to a 2.07% elevation in CK levels, while the Atorvastatin treatment group showed a 1.9% increase in CK values. The differences in HDL-C, ALT, and CK levels between the two groups were not statistically significant ($p>0.05$). ***Conclusion:*** The study revealed that combination therapy of Atorvastatin with Ezetimibe is more effective in reducing LDL-C, TG, and total cholesterol in patients with mixed hyperlipidemia compared to Atorvastatin alone.

Key Words: Efficacy, Atorvastatin, Atorvastatin with Ezetimibe, mixed hyperlipidemic patients.

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Introduction:

Mixed dyslipidemia, marked by elevated levels of triglycerides (TGs) and low-density lipoprotein cholesterol (LDL-C), along with reduced levels of high-density lipoprotein cholesterol (HDL-C), is related to an elevated risk of coronary heart disease (CHD).[1] Disruptions in lipid parameters, including total cholesterol (TC), LDL-C, VLDL, TGs, and HDL-C, can result in dyslipidemia. Combined or mixed hyperlipidemia (CHL) is a lipid condition marked by elevated low-density lipoprotein cholesterol (LDL-C), increased triglycerides (TGs), and decreased high-density lipoprotein cholesterol (HDL-C),

which is frequently seen in patients with type-2 diabetes mellitus.[2] An increased risk of coronary atherosclerosis is strongly associated with elevated low-density lipoprotein (LDL) cholesterol.[1] LDL is the primary cholesterol-carrying lipoprotein in plasma and the underlying cause of many types of coronary heart disease.[3] LDL-C reduction in the guideline-recommended treatment target for primary and secondary prevention of cardiovascular events.[4,5] The previous guidelines established by the US National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) recommended an LDL-C target of <100mg/dl for primary prevention in individuals with multiple coronary heart disease (CHD) risk factors. For patients at very high risk, the recommended goal was an LDL-C level of <70mg/dl[6-8]. Survey studies have demonstrated that, only 67% of patients with treated dyslipidemia reach their LDL-C target level goal.[9] Statins, fenofibrate, ezetimibe, niacin, and other lipid-lowering medications are used to treat such condition.[10]

Atorvastatin, a frequently prescribed statin, is generally well-tolerated and effectively reduces LDL-C levels by an average of 37-53%. Its hyperlipidemic action stems from inhibiting hydroxymethyl glutaryl-CoA reductase (HMG-CoA reductase) and boosting LDL-receptor activity.[11] Moreover, Atorvastatin improves the lipid profile in other ways, such as by increasing HDL-C and lowering TG levels to some extent. Several trials have shown that the incidence of major coronary events is reduced by around 30% with statin therapy.[12,13] In a recent meta-analysis, it was revealed that decreasing LDL-C levels with statins leads to a 22% reduction in the occurrence of myocardial infarction, coronary death, ischemic stroke, and coronary revascularization for every 39 mg/dl decrease in LDL-C levels.[14] Variability in the response to statin therapy, particularly in terms of LDL-C lowering, is associated with factors such as age, gender, race, genetic and metabolic profiles, existing medical conditions, a history of vascular disease, and abnormalities in lipoprotein levels[15,16]. Despite statins being the primary recommended treatment for lowering LDL-C levels, a significant number of patients fail to achieve sufficient reduction solely through statin therapy.[17] In high-risk individuals, lowering LDL-C can be achieved through various methods recommended by several guidelines, including increasing statin dosage, switching to a more potent statin, or adopting combination therapy.

Ezetimibe is an innovative cholesterol absorption inhibitor. It works by selectively blocking the activity of the Niemann-Pick C1 like 1 (NPC1L1) sterol transport protein, thereby inhibiting the absorption of both dietary and biliary cholesterol in the small intestine.[18] It lowers the LDL-C by about 18% following a once-daily 10mg dose[3]. Several studies have examined the combined impact of inhibiting cholesterol synthesis with atorvastatin and blocking cholesterol absorption with ezetimibe across diverse patient populations. The addition of ezetimibe to ongoing atorvastatin therapy results in significantly greater attainment of LDL-C targets and reductions in other key lipid parameters. This supplementary reduction in LDL-C ranges from 14–20% compared to increasing the dosage of atorvastatin. While ezetimibe monotherapy leads to a 20% reduction in LDL-C and is well tolerated, only 9% of patients achieve their LDL-C targets. However, when atorvastatin is combined with ezetimibe, LDL-C is reduced by 37% compared to baseline values, with a higher rate of LDL-C target achievement observed.[19]

A fixed-dose combination of ezetimibe and atorvastatin, a statin known for its higher potency compared to others, has recently gained approval from the US-FDA. This combination offers an alternative treatment for high-risk patients who fail to achieve the recommended LDL-C levels with statin monotherapy. The combination of ezetimibe and statins decreased the occurrence of clinical adverse effects (AEs), encompassing serious drug-related issues and predetermined AEs of interest (such as gastrointestinal, gallbladder, and hepatitis-related allergic reactions/rashes), as well as laboratory AEs such as repeated elevations in Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Creatine kinase (CK) to a level comparable with that observed with placebo and statins.[20]

Methodology

Study design and settings: A prospective interventional study was conducted to compare the efficacy of Atorvastatin and Atorvastatin combined with Ezetimibe among mixed hyperlipidemic patients in the outpatient department (OPD) of the Department of Cardiology, in collaboration with the Department of Medicine at Sylhet MAG Osmani Medical College Hospital, Sylhet, Bangladesh from February to November, 2023. Patients aged 30-70 years with recently diagnosed hyperlipidemia (total cholesterol >200 mg/dl, triglycerides >150 mg/dl,

LDL-C >100 mg/dl, and HDL-C <40 mg/dl), as per the criteria outlined by the National Cholesterol Education Program (NCEP-ATP III), were conveniently selected for initial screening. During the initial screening visit, patients' medical histories were recorded through interviews, followed by a comprehensive physical examination and laboratory assessments. All laboratory tests were conducted after an overnight fast, measuring serum lipid parameters along with fasting blood sugar (FBS), hemoglobin (Hb%), serum creatinine, thyroid-stimulating hormone (TSH), alanine aminotransferase (ALT), and Creatine kinase (CK). Patients with familial hypercholesterolemia, pregnancy, or breastfeeding were excluded. Additionally, patients with liver dysfunction (ALT ≥1.5 times the upper limit of normal), renal dysfunction (s. creatinine >1.6mg/dl), thyroid dysfunction, myopathy, critical illnesses, malignancies, or those on concurrent medications known to affect lipid levels such as beta blockers, verapamil, thiazides, and oral contraceptive pills (OCPs) were also excluded from the study. Then after a 5 week run in on Atorvastatin 10mg/day, subjects who were not at the LDL-C treatment target of 100mg/dl were selected for this study. In addition to Ezetimibe 10mg, stable atorvastatin 10mg or doubling Atorvastatin to 20mg.

Patient's selection criteria: A total of 76 patients were interviewed using a pre-tested, semi-structured questionnaire. These patients were divided into two groups. Group-I received a combination of Tab. Atorvastatin 10mg plus Tab. Ezetimibe 10mg, while group-II received Tab. Atorvastatin 20mg once daily at night for 12 weeks. After 12 weeks, plasma lipid parameters (TC, TG, HDL, and LDL) and non-lipid parameters (ALT, and CK) of both groups were taken as baseline values during randomization. Patients were assessed after 12 weeks, and again, their lipid parameters and non-lipid parameters were measured. Patients were advised to report immediately if they experienced unusual muscle soreness or pain throughout the study. All the subjects who entered the run-in period were asked to follow the NCEP Step-I diet. Information regarding the efficacy and tolerability was recorded in the given case record form during follow-up. Efficacy was assessed based on laboratory values of the lipid profile. Tolerability assessments were based on patient complaints, physical examinations, and clinical laboratory evaluations of hepatic transaminase (ALT) elevation >3xULN or CK elevation >10xULN. A total of 76 subjects were initially screened for participation in the study. Of these, 68 patients underwent a 5-week run-in period with atorvastatin 10mg, and 63 patients met the inclusion criteria and were randomly assigned to either Atorvastatin 10mg+ Ezetimibe 10mg or Atorvastatin 20mg. In Group-I (Atorvastatin 10mg with Ezetimibe 10mg), three patients dropped out of the study. One patient did not adhere to medication regularly, one experienced mild muscle pain, and one withdrew consent to participate. Similarly, in Group-II (Atorvastatin 20mg), two patients were withdrawn from the study due to irregular medication intake. Consequently, data from 30 participants in Group-I and 28 participants in Group-II were used for analysis. These participants tolerated both study medications well and completed the study. No significant adverse events were recorded during the study.

Data collection procedures: Data were coded, entered, edited, and cleaned cautiously, and then exported into SPSS v23 (Armonk, USA). Continuous variables were computed using measures of central tendency and dispersion such as mean, percent, and standard deviation. For significance, the independent sample 't' test was used to compare the mean of continuous variables. At the 95% confidence level, a p-value <0.05 indicated a significant association. The findings were presented in tables and chart.

Ethical approval: Each participant provided informed written consent. Data confidentiality was thoroughly maintained, and unauthorized access to data was prohibited. All procedures were carried out in accordance with the ethical norms outlined in the 1964 Declaration of Helsinki. Ethical approval for the study was obtained from the approved by the 'Institutional Review Board' (IRB) of Sylhet Women's Medical College, Sylhet, Bangladesh.

Results

In Group-I and Group-II, the mean ages of the patients were 51.1±8.4 and 52.3±4.2 years, respectively, with mean BMIs of 28.7±2.6 and 27.8±4.8 kg/m2. The male-to-female ratios in both groups were 12:18 and 13:15, respectively (Table-I and Figure-I).

Table 1: Patients profile (n=58)

Characteristics	Group-I (n=30)	Group-II (n=28)
	Mean ±SD	Mean ±SD
Mean age (in years)	51.1±8.4	52.3±4.2
BMI (in kg/m^2)	28.7±2.6	27.8±4.8
H/O medical conditions	**n(%)**	**n(%)**
Diabetes Mellitus	3(10.0%)	4(14.2%)
Hypertension	12(40.0%)	14(50.0%)
Coronary artery diseases	3(10.0%)	2(7.1%)
Currently smoker	2(6.6%)	1(3.5%)

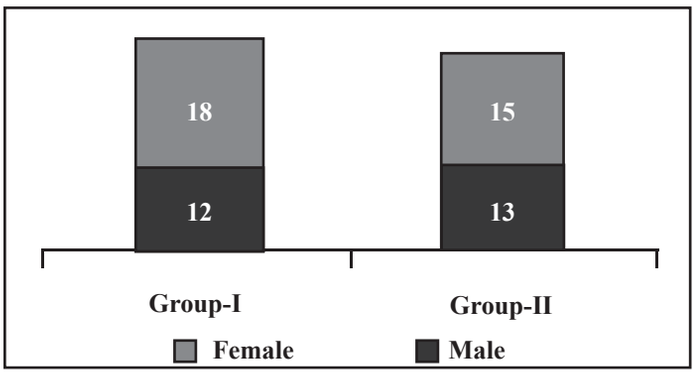

Figure-I: Male-female ratio of the both groups (n=58)

Changes in lipid profile values: At the end of 12 weeks, Group-I showed a significant decline (p<0.05) in TC (35.7%), TG (30.6%), and LDL-C (47.5%) compared to pretreatment values. HDL-C increased, although not significantly (p>0.05). At the end of 12 weeks, Group-II showed a significant decline (p<0.05) in TC (30.1%), TG (16%), and LDL-C (40.1%), with a not significant increase in HDL-C (2%) compared to pretreatment values. Comparison of changes in lipid profile between the combination group and the atorvastatin group after treatment revealed a significant reduction (p<0.05) in total cholesterol (35.7% vs. 30.1%), triglycerides (30.6% vs. 16%), and LDL-C (47.5% vs. 40.1%). (Table 2 and Table 3)

Table 2: Changes in lipid profile values among Group-I patients (n=30)

Parameters	Baseline value	After 12 weeks	Change (%)	p-value
	Mean ±SD	Mean ±SD		
TC	238.5 ± 1.1	152.7 ± 2.2	-35.7	*0.001
LDL	162.7 ± 1.6	85.4 ± 1.7	-47.5	*0.001
HDL	38.0± 8.1	41.6±8.0	+7.8	>0.05
TG	232.3±1.1	161.2±1.2	-30.6	*0.001

Independent sample 't' test was done, *Statistically significant value

Table 3: Changes in lipid profile values among Group-II patients (n=28)

Parameters	Baseline value	After 12 weeks	Change (%)	p-value
	Mean ±SD	Mean ±SD		
TC	239.6 ± 1.8	167.2±2.0	-30.1	*0.001
LDL	162.8±1.5	97.5±1.9	-40.1	*0.001
HDL	39.6± 3.9	41.9±5.3	+2.0	>0.05
TG	210.1±0.8	176.2±0.8	-16.0	*0.001

Independent sample 't' test was done, *Statistically significant value

Changes in ALT and CK values: In the combination therapy group, ALT levels increased by 4.6%, compared to a 3.8% increase with Atorvastatin treatment alone. Although a greater elevation in ALT levels was found in the combination therapy group, the differences in ALT values between the two groups were not statistically significant (p>0.05). (Table 4)

Table 4: Changes in Alanine Aminotransferase (ALT) in both groups (n=58)

Groups	Baseline value	After 12 weeks	Change (%)	p-value
	Mean ±SD	Mean ±SD		
Group-I	29.8±5.6	31.2±4.3	4.6	>0.05
Group-II	30.9±4.4	32.2±4.3	3.8	>0.05

Independent sample 't' test was done

Combination therapy resulted in a 2.07% elevation in CK levels, whereas the Atorvastatin treatment group showed a 1.9% increase in CK values. Although a greater rise in CK levels was observed in the combination group, the differences in CK values between the two groups were not statistically significant (p>0.05). (Table 5)

Table 5: Changes in Creatine Kinase (CK) in both groups (n=58)

Groups	Baseline value	After 12 weeks	Change (%)	p-value
	Mean ±SD	Mean ±SD		
Group-I	89.5±1.4	91.4±5.3	2.1	>0.05
Group-II	82.6±2.4	84.2±4.1	1.9	>0.05

Independent sample 't' test was done

Discussion

Dyslipidemia is the commonest cause of cardiovascular disease, and its prevalence has been raising globally.[11] Statins are the most commonly used therapy to treat elevated TC and LDL-C, which effectively lowers the risk of cardiovascular events.[17] In patients with primary

hypercholesterolemia, Ezetimibe is also reported to reduce LDL-C by 15-25% with favorable effects on TG and HDL-C. Ezetimibe and Atorvastatin combination therapy effectively target the dyslipidemia associated with mixed hyperlipidemia.[3]

At the end of 12 weeks, Group-I exhibited a significant decrease ($p<0.05$) in total cholesterol (35.7%), triglycerides (30.6%), and LDL-C (47.5%) compared to baseline values. There was an increase in HDL-C, but not significantly ($p>0.05$). Similarly, Group-II also demonstrated a significant decrease ($p<0.05$) in total cholesterol (30.1%), triglycerides (16%), and LDL-C (40.1%) at the end of 12 weeks, along with a non-significant increase in HDL-C (2%). Comparison of lipid profile changes between the combination therapy group and the atorvastatin group post-treatment indicated a significant reduction ($p<0.05$) in total cholesterol (35.7% vs. 30.1%), triglycerides (30.6% vs. 16%), and LDL-C (47.5% vs. 40.1%).

A similar study was conducted to assess the effects of Atorvastatin alone or in combination with ezetimibe in hyperlipidemic patients. This study randomized individuals to receive Atorvastatin 10mg/day plus ezetimibe 10mg/day or Atorvastatin 20mg/day. Statistically significant findings comparing combination therapy with atorvastatin monotherapy included mean changes from baseline in total cholesterol (combination -31.1%, Atorvastatin -28.2%), LDL-C (combination -48.1%, Atorvastatin -35%), and triglycerides (combination -34%, Atorvastatin -18%), along with insignificant changes in HDL-C (combination +5.4%, Atorvastatin +6.2%)21. This study suggests that combination therapy with Atorvastatin and ezetimibe is superior to atorvastatin monotherapy.

In a study, the efficacy of atorvastatin 5mg/day plus ezetimibe 5 mg/day was compared with atorvastatin 20 mg/day in patients with combined hyperlipidemia. The combination therapy resulted in a reduction of total cholesterol (TC) by 33%, LDL-C by 43%, triglycerides (TG) by 30%, and an increase in HDL-C by 9%. These changes were found to be superior to those observed with monotherapy.[22]

In the current study, there was no statistically significant difference in the change in HDL-C between the two treatment groups. However, following drug treatment, HDL-C showed a greater increase in the combination group compared to monotherapy (+7.8% vs +2.0%).

Combining ezetimibe with a statin has been shown to have an additive effect on increasing HDL-C levels.[23] Additionally, it's been reported that atorvastatin has a lesser effect on increasing HDL-C levels at higher doses[24]. The results of these two prior studies indicate that a significant increase in HDL-C was observed only with low-dose atorvastatin-ezetimibe combination therapy.

The results of our study, relating to the efficacy of lipid lowering drugs on lipid parameters, appear to be in agreement with those of the literature. The NCEP ATP III guideline recommends combined drug therapies to achieve the lipid goals for patients with mixed hyperlipidemia. Lowering LDL-C is the initial target of treatment, followed by treatments that improve the other lipid abnormalities associated with mixed hyperlipidemia.

The findings from the current study suggest that combining Ezetimibe with a low dose of Atorvastatin is highly effective in lowering LDL-C levels. However, when Ezetimibe is combined with higher doses of statins, only a minimal additional reduction in LDL-C was observed.[25] Thus, higher dose statin therapy may not be necessary in combination with Ezetimibe, considering the safety and efficacy of the low dose combinations. In a double blind clinical trial, Ballatyne et al.[25] reported that 10mg/day of Ezetimibe combined with 10mg/day of Atorvastatin had the same LDL-C reducing effect as 80mg/day of Atorvastatin alone. Our findings thus suggest that LDL-C can be better controlled by combining Ezetimibe with statin. Regarding the adverse effects of lipid lowering drugs, we noticed insignificant elevations of ALT and CK. There were no instances of elevation of ALT>3XULN as CK>10 XULN and both regimens were well tolerated. The mean levels of ALT and CK did not change significantly in either group throughout the drug treatment. The results of this study indicate that either combined therapy or monotherapy did not significantly affect the liver functions in the study population. The most common hepatic adverse reaction associated with statins is elevated liver enzymes without histopathological changes.[11] This elevation is usually asymptomatic, reversible, and dose dependent. Its incidence was 1.8% with Atorvastatin 10mg/day in the ARIANE study.[26] In the TNT study, significant hepatic cytolysis was observed in 1.2% of patients treated with high dose Atorvastatin compared with 0.2% in the low dose group.[27] According to Hansen et al.[28] Myalgia usually appears within the first 6 months of therapy, and this myalgia typically resolves after two months of stopping

treatment. In a review of 20 clinical trials, the prevalence of mild muscle pain on statins was 195 per 100,000 patients, and that of rhabdomyolysis 1.6 per 100,000 patients.[29] According to Kwang et al.[30] 0.1% of patients on statin therapy experienced myopathy with CPK levels more than 10 times the upper limit. In the ARIANE study, after 12 weeks of treatment with Atorvastatin the incidence of myalgia was 5.4% and an elevation of CPKs was observed in 3.9% of patients.[31]

The main limitation of this study is the small sample size. Patients were followed only for 12 weeks, and the impact of non-pharmacological treatment in this study was not taken into account.

Conclusion

The study demonstrated that Atorvastatin 10mg/day with Ezetimibe 10mg/day combination therapy possess more LDL reduction efficacy than Atorvastatin 20mg in reducing LDL-C, TG, and total cholesterol in patients with mixed hyperlipidemia. However, it has a lesser effect on the elevation of HDL-C. In patients with mixed hyperlipidemia, the majority of doctors nowadays prefer Atorvastatin either by itself or in combination with ezetimibe over alternative lipid-lowering drugs.

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