OPEN LABEL RANDOMIZED CONTROLLED TRIAL COMPARING THE EFFICACY OF ATORVASTATIN ALONE AND COMBINATION OF ATORVASTATIN AND EZETIMIBE IN PRIMARY DYSLIPIDEMIA

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Abstract: Introduction: Coronary artery disease (CAD) is assuming increasingly importance among the adult population as well as developing countries. Various studies have associated the direct casual relationship between CAD and dyslipidemia. Statins are the most widely used hypolipidemic drugs. Despite the proven efficacy of statin therapy, there is a significant gap between evidence based medicine and real world clinical practice. Objectives: The study was designed to evaluate the efficacy of atorvastatin alone and combination of atorvastatin and ezetimibe in patients diagnosed with primary dyslipidemia. Methods: An open labelled, randomized study enrolling 200 patients diagnosed with CAD and primary dyslipidemia was conducted in the Department of Cardiology M.S.Ramaiah Hospitals, Bengaluru. These patients were randomized to either atorvastatin 10 mg alone once daily or combination of atorvastatin 10mg and ezetimibe 10 mg once daily for 3 months. Lipid profile was analysed both at entrance as well as at the end of the study. Results: The reduction of LDL-C level between the atorvastatin alone and combination of atorvastatin and ezetimibe group from the baseline was 41.63 mg/dl and 49.98 mg/dl respectively (P <0.001). On comparing between the 2 groups the combination group had higher reduction than the atorvastatin alone group (P < 0.001). Conclusion: The combination of atorvastatin and ezetimibe is highly effective in treatment of primary dyslipidemia.

Key words: Coronary artery disease; Dyslipidemia; LDL-C; Atorvastatin; Ezetimibe.

INTRODUCTION

With globalization and industrialization, there have been changes in life style and life spans, seen all over the world. A consequence of these changes has lead to changes in the type of the disease pattern, with chronic diseases like diabetes mellitus, hypertension and dyslipidemia becoming more prevalent. It is expected that by 2020 in developing countries, non-communicable disease will account for 69% of all deaths, with cardiovascular diseases in the lead 1.

Coronary artery disease (CAD) is assuming increasing importance among the adult population in both developed and developing countries. The prevalence of CAD is showing an upward trend and has taken an “epidemic” course. CAD among the Asian Indians is more severe, diffuse, associated with serious complications and increased mortality in younger age group.

Various clinical and epidemiological studies clearly establish the link between CAD and dyslipidemia. Dyslipidemia is one of the main risk factors for the development of CAD. Indeed, there is direct relationship between serum LDL-C level and cardiovascular risk. This relationship is linear, such that reduction in serum LDL-C level results in proportionate reduction in cardiovascular risk 2.

Based on various compelling evidence, the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Cholesterol in Adults (Adult Treatment Panel 3) issued treatment guidelines in 2001, identified serum LDL-C as a causative factor for CAD and as the target for lipid lowering therapy.

Statins acts by inhibiting 3-hydroxy 3-methyl glutaryl coenzyme A (HMG-CoA) reductase, a key enzyme involved in cholesterol synthesis. Statins also increase hepatic low density lipoprotein receptor activity and cause accelerated clearance of circulating Low Density Lipoprotein Cholesterol (LDL-C), resulting in dose dependent reduction in plasma level of LDL-C. These are remarkably safe and most widely used hypolipidemic drugs 3.
Despite the proven efficacy of statin therapy, various studies documented significant gaps between evidence based medicine and “real world” clinical practice. This translates into a need to either use a higher dose of statins which might lead to a greater incidence of adverse effects (ex. elevation of liver enzymes, myopathy) or to add other lipid lowering drugs to statin therapy which could lead to greater drug intolerance or other adverse effects.

Ezetimibe inhibits intestinal absorption of cholesterol at the brush border level of the enterocyte. This results in reduction of hepatic cholesterol level and an increase in hepatic LDL-receptor expression. Ezetimibe has demonstrated a 17-20% reduction in serum LDL-C level. Ezetimibe has become a preferred add on drug with statin in patients, who require further LDL-C reduction with out an increase in adverse effects.

The present study will aim to compare the efficacy of atorvastatin alone and combination of atorvastatin with ezetimibe in patients with primary dyslipidemia.

CAD also called ischemic heart disease (IHD) has been defined as “impairment of heart function due to inadequate blood flow to the heart compared to its needs, caused by obstructive changes in the coronary circulation to the heart”.

It is the cause of 25-30% of deaths in most industrialized countries. The WHO has drawn the attention to the fact that CAD is one modern “epidemic” i.e. a disease that affects populations, not an unavoidable attribute of aging.

CAD is assuming a serious dimension in developing countries. It is expected to be the single most important cause of death in India by the year 2015. There is considerable increase in prevalence of CAD in urban areas in India during the last decade. Although, there is an increase in prevalence in rural areas, it is not that steep because life style changes have affected people in urban areas more than in rural areas.

The clinical rationale of combination therapy in dyslipidemia are to reduce the risk of the dose related side effects of statins or to improve efficacy by using medications with differing mechanisms of action to provide the potential for additive or synergistic benefits.

The greatest LDL-C reductions with statins are usually achieved at the starting dose. Each subsequent doubling of the dose generally results in only an additional 5-7% LDL-C reduction. For this reason, combining a statin with other pharmacological agents rather than titrating the dose might help to maximize patient responses. The availability of ezetimibe, a cholesterol absorption inhibitor, expands the options for controlling LDL-C levels in patients in whom NCEP ATP III goals cannot be met with lifestyle changes or drug monotherapy.

**METHODOLOGY**

**Study type:** Open label, Randomized controlled study.

**Source of data and Study population:** Patients with Primary dyslipidemia and Coronary Artery Disease attending the Out-Patient Clinic in the Department of Cardiology, M.S. Ramaiah Hospital, Bengaluru.

**Method of collection of data:** Patients attending the Out-Patient clinic were recruited based on the inclusion and exclusion criteria mentioned below.

**Inclusion criteria:**
1. Patients with Stable Coronary Artery Disease and Primary dyslipidemia.
2. Patients with LDL-C,
   a) Above 160 mg/dl in patients with no documented CAD.
   b) Above 130mg/dl in patients with documented CAD.
3. Both male and female patients.
4. Age group of 30 to 65 years.

**Exclusion criteria:**
1. Uncontrolled diabetes mellitus.
2. Severe liver dysfunction.
3. Renal failure.
4. Alcoholism.
5. Patient on steroids.
6. Dyslipidemia due to thyroid disorders, biliary diseases.

**Study procedure:** The study was conducted as per the ICH-GCP guidelines. The study protocol was approved from the Ethics Review Board. Informed consent was obtained, after fully explaining the procedure and the consequences in patients own language. The work up included a detail history taking as per the Proforma. The patients were randomized in 1:1 ratio to either of the 2 - treatment groups. Group I received Atorvastatin 10mg / once daily alone and the Group II received combination of Atorvastatin 10mg and Ezetimibe 10mg / once daily for 3 months.

Measurement of lipid values: Blood samples were collected before the randomization, with the patient fasting for at least 12 hours. Serum lipid values were analysed at Gokula metropolis research laboratory, M S Ramaiah Hospital, Bangalore.
Table-1: Methods of lipid analysis.

<table>
<thead>
<tr>
<th>Lipid parameter</th>
<th>Method of analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>Enzymatic Method – Cholesterol oxidase-peroxidase method</td>
</tr>
<tr>
<td>HDL</td>
<td>Accelerator selective detergent method</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Enzymatic method – Lipoprotein lipase method</td>
</tr>
<tr>
<td>LDL</td>
<td>( \text{TC} - (\text{HDL} + \text{TG}/5) )</td>
</tr>
<tr>
<td>VLDL</td>
<td>TG/5</td>
</tr>
</tbody>
</table>

**Follow up:** Lipid profile was repeated at the end of 3rd month and the changes in the lipid profile was compared between the 2 groups.

**Statistical analysis:** Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance. Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) and Student t test (two tailed, dependent) has been used to find the significance of study parameters on continuous scale with in each group. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

**RESULTS & DISCUSSION**

The present study was an open labeled, randomized study to evaluate the efficacy of atorvastatin alone and combination of atorvastatin and ezetimibe in patients with primary dyslipidemia. The present study involved 200 patients, 100 patients each in atorvastatin alone and combination of atorvastatin and ezetimibe group.

The study participants were between the age group of 21-80 years (TABLE 2). The mean age in the atorvastatin alone group was 55.09 years and in the combination of atorvastatin and ezetimibe group was 54.69 years.

Out of 200 patients, 33 were female and 167 were male patients (TABLE 2). In atorvastatin alone group 23 (23%) were female and 77 (77%) were male patients. In combination of atorvastatin and ezetimibe group 10 (10%) were female and 90 (90%) were male patients. The mean lipid parameters in the each treatment group were as indicated in the TABLE -3.

Table -2: Comparison of age and sex distribution

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group I (Atorvastatin)</th>
<th>Group II (Atorvastatin + Ezetimibe)</th>
<th>('P' Value )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (Mean ± SD)</td>
<td>55.09±9.11</td>
<td>54.69±10.25</td>
<td>0.776</td>
</tr>
<tr>
<td>Gender</td>
<td>Male (%)</td>
<td>77</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Female (%)</td>
<td>23</td>
<td>10</td>
</tr>
</tbody>
</table>

\*P=0.013 – Samples are not gender matched
Table 3: Effect of treatment on Lipid parameters

<table>
<thead>
<tr>
<th>Lipid variables</th>
<th>Point of study</th>
<th>Group I (Atorvastatin)</th>
<th>Group II (Atorvastatin + Ezetimibe)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (TC) (mg/dl)</td>
<td>Before</td>
<td>198.51±36.40</td>
<td>192.82±27.09</td>
<td>0.211</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>151.67±21.28</td>
<td>135.72±10.48</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td></td>
<td>Change</td>
<td>46.84±22.67</td>
<td>57.09±21.88</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>&lt;0.001**</td>
<td>&lt;0.001**</td>
<td>-</td>
</tr>
<tr>
<td>Triglycerides (TG) (mg/dl)</td>
<td>Before</td>
<td>130.67±60.86</td>
<td>125.18±47.60</td>
<td>0.478</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>100.26±38.30</td>
<td>96.24±29.32</td>
<td>0.406</td>
</tr>
<tr>
<td></td>
<td>Change</td>
<td>30.42±34.62</td>
<td>28.94±28.61</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>&lt;0.001**</td>
<td>&lt;0.001**</td>
<td>-</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>Before</td>
<td>38.56±9.53</td>
<td>42.35±8.29</td>
<td>0.003**</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>41.21±9.74</td>
<td>45.12±7.75</td>
<td>0.002**</td>
</tr>
<tr>
<td></td>
<td>Change</td>
<td>2.63±1.32</td>
<td>2.77±1.46</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>&lt;0.001**</td>
<td>&lt;0.001**</td>
<td>-</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>Before</td>
<td>130.46±27.13</td>
<td>123.58±23.58</td>
<td>0.057+</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>88.83±19.82</td>
<td>73.60±10.13</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td></td>
<td>Change</td>
<td>41.63±15.54</td>
<td>49.98±21.46</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>&lt;0.001**</td>
<td>&lt;0.001**</td>
<td>-</td>
</tr>
<tr>
<td>VLDL (mg/dl)</td>
<td>Before</td>
<td>25.04±11.06</td>
<td>26.72±9.21</td>
<td>0.245</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>20.31±8.26</td>
<td>20.76±6.29</td>
<td>0.660</td>
</tr>
<tr>
<td></td>
<td>Change</td>
<td>4.74±4.32</td>
<td>5.96±4.49</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>&lt;0.001**</td>
<td>&lt;0.001**</td>
<td>-</td>
</tr>
</tbody>
</table>

The reduction of Total Cholesterol (TC) levels between the atorvastatin alone and combination of atorvastatin and ezetimibe group, from baseline was 46.84 mg/dl and 57.09 mg/dl respectively, which was statistically significant (P < 0.001). On comparing the 2 groups, the combination group had a greater reduction than the atorvastatin alone group, which was statistically significant (P < 0.001), (FIGURE 1).
Figure 1: Bar chart showing total cholesterol changes in between the 2 groups.

The reduction of Triglycerides (TG) levels between the atorvastatin alone and combination of atorvastatin and ezetimibe group, from baseline was 30.42 mg/dl and 28.94 mg/dl respectively (P < 0.001). On comparing, the reduction in between the 2 groups was not statistically significant (P < 0.406), (FIGURE 2).

Figure 2: Bar chart showing triglycerides changes in between the 2 groups.

The mean change of High Density Lipoprotein (HDL) levels between the atorvastatin alone and combination of atorvastatin and ezetimibe group, from baseline was 2.63 mg/dl and 2.77 mg/dl respectively, which was statistically significant (P < 0.001). On comparing the 2 groups, the combination group had a greater percent of change than the atorvastatin alone group, which was statistically significant (P < 0.002), (FIGURE 3).

Figure 3: Bar chart showing High Density Lipoprotein (HDL) changes in between the 2 groups.

The reduction of Low Density Lipoprotein (LDL) levels between the atorvastatin alone and combination of atorvastatin and ezetimibe group, from baseline was 41.63 mg/dl and 49.98 mg/dl respectively, which was statistically significant (P < 0.001). On comparing the 2 groups, the combination group had a greater reduction than the atorvastatin alone group, which was statistically significant (P < 0.001), (FIGURE 4).
The reduction of Very Low Density Lipoprotein (VLDL) levels between the atorvastatin alone and combination of atorvastatin and ezetimibe group, from baseline was 4.74 mg/dl and 5.96 mg/dl respectively (P < 0.001). On comparing, the reduction in between the 2 groups was not statistically significant (P < 0.660), (FIGURE 5).

Various studies have evaluated the efficacy of atorvastatin and the combination of atorvastatin and ezetimibe in primary dyslipidemia. The results obtained from the present study are consistent with the following studies.

A multicenter, randomized, open label, active controlled, parallel study was conducted by J P D Reckless et al, to investigate the efficacy and safety profile of switching to ezetimibe/Simvastatin 10/40 mg compared with doubling the statin dose in high risk patient hospitalized for a recent coronary event. The treatment with the combination produced greater improvement in lipids with a similar safety profile compared with doubling of statin dose. A prospective, randomized, double blind, active comparator, multi center study by John J P et al, to compare the effects of 80 mg of Simvastatin either with placebo or with 10 mg of ezetimibe in hypercholesterolemic patients. The combination therapy of Simvastatin and ezetimibe produced significant decrease in LDL-C when compared to Simvastatin alone.

A 12 week, multicenter, randomized, double blind, parallel, arm study by Franklin Z et al, was conducted to assess safety and efficacy of ezetimibe added to atorvastatin versus up titration of atorvastatin to 40 mg in patients >65 years of age at risk for CAD. The addition of ezetimibe to atorvastatin produced significantly greater changes in most lipid parameters and greater attainment of prespecified LDL-C levels than doubling the atorvastatin dose.

CONCLUSION

Dyslipidemia is one of the main risk factor for the development of CAD. The relationship between serum LDL and CV risk is direct. Given the epidemic course of CAD, it is a relevant public health issue to find the add on drug to a statin, in patients who require further LDL reduction with out increase of adverse effects.

The present study demonstrates that ezetimibe added to atorvastatin brings about greater percent of change in TC, LDL and HDL.

The combination therapy helps in achieving the target cholesterol level specified for their coronary risk group given by NCEP 3. Hence the combination is highly effective than atorvastatin alone in treatment of primary dyslipidemia.
Acknowledgements

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REFERENCES