Antioxidant Effect of Atorvastatin and Rosuvastatin in Hyperlipidemic Patients: A Randomized Controlled Trial

Tonu SH¹, Dewan JF², Akhter N³, Haque ME⁴, Wahab MA⁵

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Abstract

Introduction: Hyperlipidemia is a major risk for the development of atherosclerosis leading to cardiovascular complications. Atorvastatin and rosvastatin are two widely used important members of the HMG-CoA reductase inhibitor (statins). The beneficial effects of statins on clinical events also involve lipid-independent mechanisms which include improvement of oxidative stress status.

Objective: To compare the antioxidative effect of atorvastatin and rosvastatin in patients with hyperlipidemia.

Materials and Methods: A prospective randomized single-center analytic study was carried out of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from March 2016 to August 2017 on 52 hyperlipidemic patients. After randomization patients were assigned to atorvastatin 10 mg or rosvastatin 5 mg daily for 8 weeks. Blood was collected at baseline and after the intervention to measure plasma malondialdehyde (MDA), erythrocyte reduced glutathione (GSH) (as biomarkers of oxidative stress) and serum lipid profile.

Results: The baseline characteristics of patients treated with atorvastatin and rosvastatin were almost identical. The level of plasma MDA in atorvastatin (1.35 ± 0.94 to 0.97 ± 0.64) and rosvastatin (1.56 ± 0.69 to 0.98 ± 0.38) group was significantly reduced after intervention (28.15%, p < 0.05 and 37.18%, p < 0.001 respectively) but no statistically significant difference (p > 0.05) was observed between the two statin-treated groups. Erythrocyte GSH level was increased after intervention in both atorvastatin (2.43±2.90 to 4.14 ± 4.87) group (70.37%, p < 0.01) and rosvastatin (2.76 ± 3.80 to 8.36 ± 12.93) group (202.90%, p <0.01), which was statistically significant. No significant difference was observed between the two groups (p > 0.05). Both atorvastatin and rosvastatin significantly improved serum lipid profile.

Conclusion: Both atorvastatin and rosvastatin significantly improved oxidative stress status in hyperlipidemic patients but no significant change was observed between the two statin-treated groups.

Key-words: Statin, Oxidative stress; Atherosclerosis.

Introduction

Hyperlipidemia is an abnormal elevation of lipid concentration in the blood which enhances atherosclerosis¹. Hyperlipidemia increases the production of free reactive oxygen species (ROS) which is an important risk factor for atherosclerosis². Under normal physiological condition, a balance is maintained between the generation of oxygen free radicals and antioxidant defense systems. Impairment in this equilibrium provokes a situation of oxidative stress³. Oxidative stress causes oxidation of low-density lipoprotein (LDL) to oxidized LDL (ox-LDL) in the areas of inflammation which plays a vital role in development of atherosclerosis⁴. Oxidation of LDL causes production of several by-products, such as aldehydes, like malondialdehyde (MDA) which can be detected in circulation and acts as an important biomarker for the detection of oxidative stress⁵. Statins can also exert a beneficial effect by enhancing the activity of endogenous antioxidant systems such as superoxide dismutase (SOD), glutathione (GSH) and catalase (CAT)⁶. Studies have suggested that 3-hydroxyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) reduce the incidence of cardiovascular events in hyperlipidemic patients by reduction of oxidative stress. Apart from their lipid-lowering action, statins exert some cholesterol-independent effects, also known as ‘pleiotropic effects’⁷. Several drugs are included within the statin group, among them atorvastatin and nowadays rosvastatin is widely used. The present study was planned to compare the antioxidative effects of newer emerging and promising statin rosvastatin with existing commonly used statin atorvastatin in patients with hyperlipidemia so as to guide the present treatment strategies.

Materials and Methods

This study was an 8-week, randomized, intervential, open-labeled trial. This trial was approved by the Institutional

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Results

Table-I shows the baseline demographic characteristic of all hyperlipidemic patients. There were total 21 males and 31 females. Considering demographic characteristics, there was no significant difference at baseline parameter between atorvastatin and rosuvastatin treated groups. Before administration of atorvastatin and rosuvastatin, the plasma MDA level (mean±SD) in the respective group was 1.35±0.94 μmol/L and 1.56±0.69 μmol/L. After 8 weeks of drug administration, the same parameter was changed to 0.97±0.64 μmol/L in the atorvastatin group and 0.98±0.38 μmol/L in rosuvastatin group (Table-II). This change was statistically significant (P<0.020 and P<0.001 respectively, Table-II) but after intervention no statistically significant difference was found in between two groups (P=0.932, Table-II) the mean decrease (%) in plasma MDA in the atorvastatin-treated group was 28.15% and in rosuvastatin-treated group was 37.18% (Table-II). At baseline, the erythrocytic GSH level (mean±SD) in atorvastatin and rosuvastatin treated group was 2.43±2.90 mg/gm of Hb and 2.76±3.80 mg/gm of Hb respectively. After 8 weeks of drug administration, the erythrocytic GSH level was increased to 4.14±4.87 mg/gm of Hb in the atorvastatin group and 8.36±12.93 mg/gm of Hb in rosuvastatin group (Table-II). This change was statistically significant (P=0.006 and P=0.002 respectively, Table-II). Again no statistically significant difference was found after intervention in between the statin-treated groups (P=0.197, Table-II). The mean increase (%) in erythrocytic GSH in the atorvastatin-treated group was 70.37% and in rosuvastatin-treated group was 202.90% (Table-II). The level of serum total cholesterol in atorvastatin group was significantly reduced after intervention (from 257.51±21.82 mg/dL to 161.60±39.59 mg/dL, 37.24 %, P < 0.001, Table-III) and also in rosuvastatin group (from 262.50±38.72 mg/dL to 154.55±35.47 mg/dL, 41.12 %, P<0.001, Table-III) but no statistically significant difference (P = 0.503, Table-III) was observed between the two statin treated groups. Serum triglyceride level was reduced from 199.71±80.65 mg/dL to 165.61±75.47 mg/dL (17.07 %, P=0.046, Table-III) in atorvastatin group and from 198.89±56.03 mg/dL to 145.59±64.97 mg/dL (26.80%, P<0.001, Table-III) in rosuvastatin group which was statistically significant. No significant difference was observed between the two groups (P=0.312, Table-III). The serum LDL-C level was reduced significantly from 178.16 ± 20.01 mg/dL to 89.11±35.17 mg/dL, 49.98 %, P<0.001 and from 181.57±32.10 mg/dL to 85.91±35.45 mg/dL, 52.68 %, P<0.001 (Table-III) in atorvastatin and rosuvastatin treated group respectively. No statistically
significant difference (P=0.749, Table-III) was observed between the two groups. Both atorvastatin and rosuvastatin reduced serum HDL-C level (from 39.40 ± 9.56 mg/dL to 39.37 ± 11.51 mg/dL, 0.8% decrease, P=0.990) and from 41.14±7.81 mg/dL to 40.41±9.11 mg/dL, 1.77% decrease, P=0.696 for atorvastatin and rosuvastatin group respectively, Table-III) but this reduction was not statistically significant. Intergroup difference was not significant (P=0.721, Table-III). Both atorvastatin and rosuvastatin were well tolerated by patients of the present study. 2 patients in atorvastatin group complained of abdominal discomfort and headache and 1 patient in rosuvastatin group complained of constipation. No serious adverse effects were seen in both the groups that needed a dose adjustment or withdrawal of the drug.

**Table-I:** Demographic characteristics of both groups before intervention

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Atorvastatin Group (n=27)</th>
<th>Rosuvastatin Group (n=25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (Mean±SD)</td>
<td>46.07±10.47</td>
<td>44.12±8.84</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (22.22%)</td>
<td>15 (60%)</td>
<td>&lt;0.014</td>
</tr>
<tr>
<td>Female</td>
<td>21 (77.78%)</td>
<td>10 (40%)</td>
<td></td>
</tr>
<tr>
<td>Body weight in kg (Mean±SD)</td>
<td>69.74±9.51</td>
<td>66.84±8.67</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Blood pressure (Mean±SD)</td>
<td>131.78±16.32</td>
<td>132.20±20.84</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Systolic</td>
<td>81.48±9.88</td>
<td>85.80±11.69</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13(48.15%)</td>
<td>18(72%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>02(7.41%)</td>
<td>02(8%)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

n = number of patients in each group, values are expressed as mean ± SD, figures in the parentheses indicate corresponding percentage, \( \phi \) = Chi-squared (\( \chi ^2 \)) was done to analyze the data, *data were analyzed by using an unpaired t-test.

**Table-II:** Oxidative stress biomarkers at baseline and after intervention

<table>
<thead>
<tr>
<th>Variables</th>
<th>Atorvastatin Group (n=27)</th>
<th>Rosuvastatin Group (n=25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA (( \mu )mol/L)</td>
<td>1.35±0.94</td>
<td>1.56±0.69</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>GSH (mg/gm of Hb)</td>
<td>2.43±2.90</td>
<td>2.76±3.80</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

n=number of patients in each group, values are expressed as mean±standard deviation (SD), before=at baseline, after=after intervention, MDA=malondialdehyde, GSH = erythrocytosed glutathione, p= in each group as compared to baseline (MDA by paired t-test and GSH by Wilcoxon signed rank test), p*=inter group comparison at baseline (MDA by unpaired t-test and GSH by Mann-Whitney U test), p**=inter group comparison after intervention (MDA by unpaired t-test and GSH by Mann-Whitney U test).

**Table-III:** Effect on serum lipid profile at baseline and after intervention

<table>
<thead>
<tr>
<th>Variables</th>
<th>Atorvastatin Group (n=27)</th>
<th>Rosuvastatin Group (n=25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mg/dL) (Mean±SD)</td>
<td>257.51±21.82</td>
<td>262.50±38.72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG (mg/dL) (Mean±SD)</td>
<td>199.71±80.65</td>
<td>198.89±56.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C (mg/dL) (Mean±SD)</td>
<td>178.16±20.01</td>
<td>181.57±32.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C (mg/dL) (Mean±SD)</td>
<td>39.40±9.56</td>
<td>41.14±7.81</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

n=number of patients in each group, values are expressed as mean±SD, before=at baseline, after=after intervention, TC=total cholesterol, TG=triglyceride, LDL-C=low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol, p= in each group as compared to baseline (paired t-test), p*=intergroup comparison at baseline (unpaired t-test), p**=intergroup comparison after intervention (unpaired t-test).

**Discussion**

Among many risk factors of cardiovascular disease hyperlipidemia is considered as the major. Two well-known and widely used drugs of the lipid-lowering group HMG-CoA-reductase inhibitors (statins) are atorvastatin and rosuvastatin. The present study was designed to compare the anti-oxidative effect of atorvastatin and rosuvastatin in patients with hyperlipidemia. VOYAGER meta-analysis data suggested that each rosuvastatin dose is equivalent to 3-3.5 time higher for atorvastatin regarding the reduction of LDL-C%. This would indicate that 5 mg rosuvastatin equivalent to 15-20 mg of atorvastatin. Another 12 weeks study shows with both rosuvastatin (5 mg) and rosuvastatin (10 mg) significantly reduced TC and LDL-C compared with atorvastatin (10 mg) treated patients.
In this study, the marker of lipid peroxidation (plasma MDA) and oxidative defense of the body (erythrocyte GSH) was measured as markers of oxidative stress in hyperlipidemic patients. Polyunsaturated lipid peroxidation produces a wide variety of oxidation products among which MDA has been widely used for many years as a convenient biomarker of oxidative stress\textsuperscript{24,25}. The high levels of plasma MDA at baseline in both atorvastatin and rosuvastatin treated groups of the present study (Table-II) correspond with the study done by Yang RL et al where elevated concentrations of plasma MDA levels continued to rise with the progression of hyperlipidemia\textsuperscript{3}. In the present study, both atorvastatin and rosuvastatin significantly reduced plasma MDA level (p < 0.05 and p < 0.001 respectively (Table-II) after 8 weeks of treatment. This would suggest that both atorvastatin and rosuvastatin exert anti-oxidant effects. No statistically significant difference (p > 0.05, Table-II) were observed between the two statin-treated groups. A similar study done by Li J et al had shown that plasma MDA level reduced significantly (p < 0.05) after 12 weeks of treatment with atorvastatin (10 mg) and its antioxidant effect was stronger (p > 0.05) than that of simvastatin 20 mg\textsuperscript{15}. This is probable that the antioxidant effect of atorvastatin was responsible for the significant reduction in MDA levels. A study in dyslipidemic rabbits has suggested that both atorvastatin (10 mg) and rosuvastatin (2.5 mg) were equally effective in reducing lipid peroxidation (measured by tissue MDA) and that no statistical difference was observed between the groups\textsuperscript{26}. These findings appear similar to present study where both atorvastatin and rosuvastatin had decreased the elevated levels of plasma MDA. Although in the present study rosuvastatin is not significantly superior statistically, but while percentage reduction in MDA was considered, rosuvastatin reduced plasma MDA levels to a greater extent compared to that of atorvastatin.

A complex antioxidant defense system (AODS) is present in the human body which includes SOD, GPx, CAT and also includes non-enzymatic antioxidants such as GSH\textsuperscript{27}. Glutathione peroxidase (GPx) converts lipid peroxides to nontoxic form where concomitant oxidation of GSH into the oxidized form glutathione disulfide (GSGG) occurs and protect cells from oxidative damage\textsuperscript{28,25,26}. Study done by Hadi NR et al has reported that serum GSH levels had increased significantly (p < 0.01) in dyslipidemic type 2 diabetic patients following 60 days of treatment with atorvastatin (20 mg)\textsuperscript{17}. This observation is indicative of a significant anti-oxidant effect of atorvastatin. A significant increase of erythrocyte GSH levels in both atorvastatin and rosuvastatin treated group (p < 0.01 and p < 0.01 respectively, Table-II) were also observed in the present study. The level of GSH was increased in both groups after intervention but no significant difference was observed between the two groups (p >0.05, Table-II). This indicates that both atorvastatin and rosuvastatin contain the anti-oxidant property and again enhances the statement that perhaps both drugs possess anti-oxidant properties of similar magnitude. The present study has also observed the beneficial effects of atorvastatin and rosuvastatin on serum lipid profile. Both of them significantly reduced serum TC, TG and LDL-C level significantly after drug treatment (Table-III) which is consistent with the study done by Khurana S, Kilit C and Adsule SM et al\textsuperscript{13,18,27}.

**Conclusion**

In this trial both atorvastatin and rosuvastatin were effective in reduction of oxidative stress and serum LDL-C level in hyperlipidemic patients. When antioxidative effect was assessed by percentage, rosuvastatin demonstrated a higher percentage of ameliorating changes compared to those of atorvastatin. Both drugs exhibited a similar safety profile. Therefore, rosuvastatin constitutes a better therapeutic option compared to atorvastatin in patients with hyperlipidemia.

**References**


