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Original Article

Comparative evaluation of the effect of statin drugs in Hyperlipidaemic patients

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ABSTRACT

Statins clearly confer substantial benefit in people with established cardiovascular (CV) disease (secondary prevention). The effectiveness of various statin drugs in hyperlipidaemic patients is evaluated in the present study. This work was undertaken to assess the effective role of statin in hyperlipidaemic patients with cardiovascular disease and comparison was made between various classes of statin drugs. The study population contained 50 subjects with hyperlipidaemia and they were administered with statin class of drugs. The administration of Rosuvastatin and Atrovastatin was found to be more effective in the treatment of hyperlipidaemic patients than that of Simvastatin and Pravastatin. Although flavostatin also had a profound effect, the dosage was high compared to other statins. Hence its effectiveness compared to Rosuvastatin and Atrovastatin need to be further investigated. Rosuvastatin and Atrovastatin can be more effective in reducing hyperlipidemia compared to other classes of statin drugs and thus further reduce the risk of cardiovascular disease in such patients. In addition to that, Rosuvastatin had less side effects in patients as compared to atrovastatin and can be defined as the most effective among the statin class of drugs.

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1. Introduction

Statins (or HMG-CoA reductase inhibitors) are a class of drug used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver. Increased cholesterol levels have been associated with cardiovascular diseases (CVD), and statins are therefore used in the prevention of these diseases [1,2,3]. Randomized controlled trials have shown that they are most effective in those already suffering from cardiovascular disease (secondary prevention), but they are also advocated and used extensively in those without previous CVD but with elevated cholesterol levels and other risk factors (such as diabetes and high blood pressure) that increase a person's risk. A number of statins are on the market: atorvastatin (Lipitor and Torvast), fluvastatin (Lescol), lovastatin (Mevacor, Altacor, Altoprev), pitavastatin

(Livalo, Pitava), pravastatin (Pravachol, Selektine, Lipostat), rosuvastatin (Crestor) and simvastatin (Zocor, Lipex) [4,5].

On average, statins can lower LDL cholesterol (so-called "bad cholesterol") by 1.8 mmol/l (70 mg/dl), which translates into a 60% decrease in the number of cardiac events (heart attack, sudden cardiac death) and a 17% reduced risk of stroke after long-term treatment [6]. They have less effect than the fibrates or niacin in reducing triglycerides and raising HDL-cholesterol ("good cholesterol"). Clinical practice guidelines generally recommend that the patient has tried "lifestyle modification", including a cholesterol-lowering diet and physical exercise, before statin use is considered; statins or other pharmacologic agents may then be recommended for patients who do not meet their lipid-lowering goals through diet and lifestyle approaches [7,8].

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1.1.Mechanism of action

Statins act by competitively inhibiting HMG-CoA reductase, the first committed enzyme of the HMG-CoA reductase pathway. HMG-CoA reductase inhibitors are a group of prescription drugs used to lower cholesterol, a white waxy substance that can stick to the inside of blood vessels, resulting in clogged arteries, heart disease, and strokes [5]. These medicines work by slowing down the body's ability to make cholesterol. Because statins are similar to HMG-CoA on a molecular level they take the place of HMG-CoA in the enzyme and reduce the rate by which it is able to produce mevalonate [11], the next molecule in the cascade that eventually produces cholesterol, as well as a number of other compounds. This ultimately reduces cholesterol via several mechanisms.

1.1.1.Inhibiting cholesterol synthesis

By inhibiting HMG-CoA reductase, statins block the pathway for synthesizing cholesterol in the liver. This is significant because most circulating cholesterol comes from internal manufacture rather than the diet. When the liver can no longer produce cholesterol, levels of cholesterol in the blood will fall. Cholesterol synthesis appears to occur mostly at night, so statins with short half-lives are usually taken at night to maximize their effect. Studies have shown greater LDL and total cholesterol reductions in the short-acting simvastatin taken at night rather than the morning, but have shown no difference in the long-acting atorvastatin [12].

1.1.2.Increasing LDL uptake

Liver cells sense the reduced levels of liver cholesterol and seek to compensate by synthesizing LDL receptors to draw cholesterol out of the circulation. This is accomplished via protease enzymes that cleave a protein called "membrane-bound sterol regulatory element binding protein", which migrates to the nucleus and causes increased production of various other proteins and enzymes, including the LDL receptor. The LDL receptor then relocates to the liver cell membrane and binds to passing LDL and VLDL particles (the "bad cholesterol" linked to disease). LDL and VLDL are drawn out of circulation into the liver where the cholesterol is reprocessed into bile salts [13,14]. These are excreted, and subsequently recycled mostly by an internal bile salt circulation.

2.Materials And Method

The population consisted of 100 male subjects divided into two groups, 50 subjects (mean age 45 – 60 years) had evidence of AMI. The other 50 subjects age and sex matched healthy subjects were studied as controls. All patients had been admitted to the Coronary Care Units (CCU) of K.G. Hospital and Postgraduate Medical Institute, Coimbatore, Tamil Nadu, India, between July 2008 and March 2010. The diagnosis of AMI was based on a history of prolonged ischemic chest pain, characteristic electrocardiogram (ECG) changes and elevated creatine kinase isoenzyme MB (CK-MB) and troponin T within 12 h after the onset of pain.

Hypertension was defined as a diastolic blood pressure ≥ 90 mm Hg, systolic blood pressure ≥ 140 mm Hg, or a self-reported use of an antihypertensive drug. Cardiovascular disease was diagnosed by angiography, ECG, sinterigraphy and effort test, or self-reported use of a β -blocker, angiotensin I converting enzyme (ACE) inhibitor and/or diuretic drug. The patients who had total cholesterol level of >220 mg/dL or triglycerides concentration >200 mg/dL, or receiving lipid lowering drugs were defined as having hyperlipidemia. No subject (patients or controls) was taking antioxidant or vitamin supplements, probucol, allopurinol, quinidine, disopyramide, or other drugs known as affecting serum lipid peroxidation and antioxidant values. Oral consent was obtained from the patients' relatives and normal subjects, prior to study.

2.1.Blood collection

Blood samples were collected by venous puncture in heparinized tubes and the plasma was separated by centrifugation at 1000 g for 15 min.

2.2.Estimation of cardiac biomarkers

Determination of lipid profile, Liver Function Test, CK and CK MB was measured by Hitachi-912 instrument.

2.3. Main evaluation

Fasting blood sample were obtained from patient, fasting concentration of following are going to measure the following parameters- LDL-C, HDL-C, TG, TC, LDL-C/HDL-C, TC/HDL-C, LP (a), APOB, APOA-1 and cardiac markers like Troponin and CPK in patients patient taking (atorvastatin 20 no) 10 mg, Patient taking (pravastatin 20 no)-10mg, Patient taking (simvastatin 20 no)-10mg, Patient taking (fluvastatin 20 no)-20mg.

Liver Function test was also evaluated for the same.

2.4. Statistical analysis

All data were expressed as mean \pm SD. The statistical significance was evaluated by the Student's 't' test using Statistical Package for the Social Sciences (SPSS Cary, NC, USA) version 10.0.

3.Result

Demographic data of hyperlipidaemia subjects are shown in Table 1. The mean age limit was 45.6 ± 9.0 in hyperlipidaemia patients. The body mass index (BMI) in hyperlipidaemia patients was 27.7 ± 2.0 . Blood Pressure systolic blood pressure was significantly high ($p < 0.05$) in patients groups.

Table 1. Demographic characteristics of Hyperlipidemia patients and control subjects

Demographic characteristics	Control	Hyperlipidaemia
Age Range (Years)	20 to 75	20 to 75
Age (Mean \pm S.D) years	44.6 \pm 9.0	45.6 \pm 9.0
Body mass index (Mean \pm SD), kg/m ²	23.2 \pm 3.7	27.7 \pm 2.0
Systolic blood pressure (mm of Hg)	110 \pm 9	128 \pm 10
Diastolic blood pressure (mm of Hg)	83 \pm 5	90 \pm 7

Table 2. Summary of Mean Baseline Characteristics (all patients randomized to treatment)

Parameters (mg/dl)	Patients with hyperlipidemia groups				
	Atorvastatin Dose 10mg	Rosuvastatin Dose 10mg	Simvastatin Dose 10mg	Pravastatin Dose 10mg	Fluvastatin Dose 20mg
Total Cholesterol	234 ± 11.3	230±11.0	272 ± 15.7	240 ± 10.8 [†]	200 ± 13.8 ^{***a}
Triglycerides	180 ± 14.3	176±13.9	205 ± 13.3	179 ± 14.8 ^{NS}	175 ± 15.6 ^{**NS}
HDL Cholesterol	39 ± 1.5	45±1.9	41 ± 1.0	40 ± 1.2 ^{NS}	42 ± 1.1 ^{*NS}
LDL Cholesterol	175 ± 10.1	170±8.6	217 ± 10.3	179 ± 9.3 ^{NS}	150 ± 12.2 ^{***a}
VLDL cholesterol	32 ± 2.0	33±1.8	37 ± 2.3	31 ± 2.2 ^{NS}	28 ± 2.1 ^{***a}
Apolipoprotein-B	196 ± 10.0	178 ± 8.5	180 ± 9.5	181 ± 9.5 ^{NS}	172 ± 8.1 ^{***a}
Apolipoprotein-AI	140 ± 7.9	143 ± 7.2	150 ± 8.0	156 ± 7.7 [†]	163 ± 7.7 ^{***a}
Lipoprotein (a)	42 ± 7.4	43 ± 7.3	41 ± 7.9	40 ± 7.5 ^{NS}	38 ± 7.1 ^{**a}
CK (IU /L)	53 ± 17	82 ± 23	89 ± 20	99 ± 23 [†]	100 ± 22 ^{***a}
CK-MB (IU/ L)	12.5 ± 2.8	14.2 ± 3.2	15.5 ± 3.8	22.5 ± 7.5	27.5 ± 9.1
Bil-T	0.79 ± 0.8	0.70±0.7	1.29 ± 0.5	1.33 ± 0.6	1.53 ± 0.51
Total protein (g/dl)	7.5 ± 0.6	7.9±1.0	7.1 ± 1.1	6.8 ± 1.6	6.9 ± 1.8
Albumin (g/dl)	4.2 ± 1.2	4.7±1.3	3.9 ± 1.0	3.7 ± 1.5	4.4 ± 1.6
SGOT	28.5 ± 7.8	26±6.2	32.5 ± 7.2	52.5 ± 10.5	67.5 ± 19.5
SGPT	39.5 ± 9.2	35±5.2	47.5 ± 10.2	72.5 ± 15.6	87.5 ± 14.1
ALP	65.5 ± 10.8	63.5±8.6	78.5 ± 11.2	81.5 ± 10.5	128.5 ± 17.3

Values are given as mean ± S.D from fifty subjects in hyperlipidemia group.

Patients with hyperlipidemia groups:

Atorvastatin 20mg compared with Simvastatin 10 mg (*p<0.05, **p<0.01, ***p<0.001)

Atorvastatin 20mg compared with Simvastatin 20 mg (†p<0.05, ††p<0.01)

Atorvastatin 10mg compared with Simvastatin 20mg (‡p<0.05) NS-Not significant

Total cholesterol level was lowered in patients administered with 10 mg of simvastatin (dose-10mg) when compared to the intake of other statins [15]. The TG levels were also considerably reduced in case of intake of simvastatin (10mg) and fluvastatin (20mg) [16]. The HDL level had no significant increase or decrease with intake of any of the statin drugs. The LDL levels went lower with the intake of fluvastatin (20mg) and simvastatin (10mg). Apolipoprotein-B level was higher in case of administration of atorvastatin (10mg) [17] and apolipoprotein A-2 level was higher with the administration of pravastatin (10mg) and fluvastatin (20mg).

Lipoprotein increased with intake of atorvastatin. Atorvastatin also lowered the administration of CK and CK-MB. Atorvastatin also markedly increased the total protein level and lowered the level of SGOT, SGPT and Alkaline Phosphatase (ALP) [18,19].

4. Discussion

Cholesterol has been singled out as the primary factor in the development of atherosclerosis. HDL is regarded as one of the most important protective factors against arteriosclerosis. HDL's protective function has been attributed to its active participation in the reverse transport of cholesterol. Numerous cohort studies

and clinical trials have confirmed the association between a low HDL and an increased risk of coronary heart disease [20,21]. The concentration of LDL correlates positively whereas HDL correlates inversely to the development of coronary heart disease. Smokers have significantly higher serum cholesterol, triglyceride, and LDL levels, but HDL is lower in smokers than in non-smokers. Evidence suggests that oxidatively modified LDL contribute to the pathogenesis of atherosclerosis. Increased oxidative stress and the generation of the free oxygen radicals can result in modification of LDL to oxidized LDL that could lead to atherosclerotic lesions[20].

CK and more particularly its isoenzyme CK-MB still have a formal place in defining myocardial infarction. These enzymes normally exist in cellular compartment and leak out into the plasma during myocardial injury due to disintegration of contractile elements and sarcoplasmic reticulum.

An elevated apolipoprotein B-apolipoprotein A-I (apo B- apo A-I) ratio is a risk factor for future coronary artery disease (CAD). It is not known whether this ratio is better than traditional lipid values for risk assessment and prediction and whether it adds predictive value to the Framingham risk score. Several mechanisms have been proposed to explain the relationship between Lp(a) and heart disease. Apo(a) has a sticky adhesive nature, making it easy to attach LDL, calcium and other components into an atherosclerotic plaque on the blood vessel wall (endothelium). Lp(a) has been associated with endothelial dysfunction as well. Due to its structural similarity with plasminogen, Lp(a) competes for binding with fibrin, thereby inhibiting the breakdown of fibrin. This action could promote blood clot formation. Finally, Lp(a) activates immune cells including monocytes and macrophages, and could induce inflammation. All of these effects help to induce plaque formation, and to promote clot formation after the plaque is ruptured. Apparently, Lp(a) is attracted to the artery wall by means of Lysine Binding Sites that become exposed when the endothelial wall is damaged[21].

Cardiovascular disease (CVD) is ranked as the number one cause of mortality and is a major cause of morbidity worldwide. Reducing high blood cholesterol, which is a risk factor for CVD events, is an important goal of medical treatment. Available for almost 2 decades, the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, have emerged at the forefront of preventive drugs for cardiovascular disease because of a substantial clinical trial database demonstrating that statins reduce the risk for coronary artery disease morbidity and death across a broad range of at-risk patient cohorts.

In the present administration of 10 mg of simvastatin was found to be most effective in reducing the level of triglycerides. The administration of statin did not contribute to a significant increase in HDL levels. Simvastatin also considerably reduced the LDL level in hyperlipidaemic patients. Apolipoprotein B level was considerably reduced by the administration of simvastatin and Apolipoprotein A-1 was reduced by intake of atorvastatin. Atorvastatin also markedly reduced the level of CK and CK-MB isoenzymes, which are regarded as efficient markers of cardiovascular diseases [22].

Atorvastatin had a profound effect on the liver function test markers where it led to an increase in total protein and albumin level and SGPT and SGOT was markedly reduced.

In short, the administration of rosuvastatin and atorvastatin was found to be more effective in the treatment of hyperlipidaemic patients than that of pravastatin. Although flavostatin also had a profound effect, the dosage was high compared to other statins. Hence its effectiveness compared to rosuvastatin and atorvastatin need to be further investigated.

5. Conclusion

Rosuvastatin and Atorvastatin can be more effective in reducing hyperlipidemia compared to other classes of statin drugs and thus further reduce the risk of cardiovascular disease in such patients. In addition to that, Rosuvastatin had less side effects in patients as compared to atorvastatin and can be defined as the most effective among the statin class of drugs.

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