Original Article

To compare the effects of Terminalia arjuna with Rosuvastatin on total cholesterol and low density lipoprotein cholesterol

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ABSTRACT

Background: *In India, CVD is a leading cause of death. Among the modifiable risk factors, hyperlipidemia is one of the important factors. Therefore lowering cholesterol level is a key factor in controlling this disease.*

Objectives: *To compare the effect of Terminalia arjuna, an indigenous drug with Rosuvastatin on serum total cholesterol and low density lipoprotein cholesterol levels, in patients of either sex with dyslipidemia.*

Material and methods: *An open prospective randomized controlled study was conducted in on 60 patients for the duration of 12 weeks. Patients were distributed into two groups of 30 patients each. Group I was given Rosuvastatin 10 mg daily and group II was given capsules containing bark powder of T.arjuna 500 mg twice daily. Patients TC and LDL-C levels were performed at baseline and then repeated at 4 weeks, 8 weeks and 12 weeks. The results of both the therapies were then compared and statistically analyzed.*

Results*: T.arjuna leads to greater reduction in mean TC level than Rosuvastatin (-14.06±8.07% vs -10.10±5.39%), (-24.73±10.69% vs -19.42±9.98%) and (-27.89±9.25% vs -24.74±10.02%) at 4, 8 and 12 weeks respectively. The difference between both the groups was statistically non-significant (p>0.05) at 4, 8 and 12 weeks. The reduction in mean LDL-C level was also greater with T.arjuna as compared to Rosuvastatin.*

Conclusion: *Both Rosuvastatin and T.arjuna were effective in causing significant decrease in serum TC and LDL-C levels, but T.arjuna had a slight edge over Rosuvastatin as it showed greater reduction in TC and LDL-C levels as compare to Rosuvastatin. And was found to be safe and well tolerated.*

Keywords: *Terminalia arjuna, Rosuvastatin, total cholesterol, low density lipoprotein, cholesterol*

Introduction

Dyslipidemia is a disorder of lipoprotein metabolism, including lipoprotein overproduction or deficiency. Dyslipidemias may be manifested by elevation of the total cholesterol, the "bad" low-density lipoprotein (LDL) cholesterol and the triglyceride concentrations, and a decrease in the "good" high-density lipoprotein (HDL) cholesterol concentration in the blood. [1] Plasma lipids are transported in complexes called lipoproteins. Metabolic disorders that involve elevations in any lipoproteins species are termed hyperlipoproteinemia or hyperlipidemia. [2] Current ATP III guidelines recommend lipid screening in all adults >20 years of age. The screen should include a fasting lipid profile (TC, TG, LDL-C, and HDL-C) repeated every 5 years. [3] Although treatment of hyperlipidemia in the context of prevention of CVD has largely been focused on the management of total plasma cholesterol and LDL-C levels, a number of recent studies have reported associations between TG levels and CVD. [4] The increased prevalence of risk factors for CVD and related chronic diseases in developing countries includes tobacco use, unhealthy dietary habits and reduced physical activity, due to significant global

changes in behaviour and lifestyle, leading to increased blood lipids levels and hypertension. These changes now threaten once-low-risk regions, a shift that is accelerated by industrialization, urbanization and globalization. [5] The potentially devastating effects of these trends are magnified by a deleterious economic impact on nations and households, where poverty can be both a contributing cause and a consequence of chronic diseases. The accelerating rates of unrecognized and inadequately addressed CVD and related chronic diseases in both men and women in low and middle income countries are cause for immediate action. [5]

In India 52% of cardiovascular deaths occur below the age of 70, compared with 23% in countries with established market economies.[4] In India, CVD is a leading cause of death. [6] There are large disparities in CVD mortality in different Indian states. This can be epidemiologically explained by difference in dietary consumption of fats, milk, sugar and green-leafy vegetables and prevalence of obesity. [7] IHD is the most common, serious, chronic, life-threatening illness in the United States, where 13 million persons have IHD, >6 million have angina pectoris, and >7 million have sustained a myocardial infarction. [8] In more than 90% of cases, the cause of myocardial ischemia is reduction in coronary blood flow due to atherosclerotic coronary arterial obstruction. In most cases, there is a long period of silent, slowly progressive, coronary atherosclerosis before these disorders manifest. Thus, the syndromes of IHD are only the late manifestations of coronary atherosclerosis that probably began during childhood or adolescence. [9] The risk of CAD in Indians is 3-4 times higher than white Americans, 6-times higher than Chinese, and 20 times higher than Japanese. Indians are prone as a community to CAD at a much younger age. In the western population, incidence of CAD in the young is up to 5% as compared to 12-16% in Indians. [10]

For the development of coronary artery disease there are certain modifiable and non-modifiable risk factors. These are as follows: [11]

Non-modifiable Risk Factors: Age, Sex, Family history of CVD, Genetic factors: A family history of CHD is known to increase the risk of premature death.

Modifiable Risk Factors: Smoking, Hypertension, Obesity, Diabetes mellitus: The risk of CHD is 2-3 times higher in diabetics, Physical activity/ sedentary habits, Elevated serum cholesterol.

Out of the modifiable risk factors, hyperlipidemia is most important risk factor as it has been reported that, worldwide high cholesterol levels are estimated to cause 56% of IHD. Ecological analyses of major CVD risk factors and mortality demonstrate high correlations between expected and observed mortality rates for the three main risk factors—smoking, serum cholesterol, and hypertension. [12] Statins (HMG-CoA reductase inhibitor) are most effective in reducing LDL-C. Other effects include decreased oxidative stress and vascular inflammation with increased stability of atherosclerotic lesions. [2] Statins have been shown to reduce clinical events in excess of what can be explained by altering lipid profile. Statins have been shown to possess antioxidant, anti-platelet aggregatory effects. [13] Statins have demonstrated their aptitude to lower hyper-cholesterolemia and to prevent the occurrence of arterial, coronary and cerebral events by primary and secondary prevention in patients with low or high risk to develop CAD. [14]

Elevation of serum aminotransferase activity occur in some patients, so it should be used with caution and in reduced dosage in patients with hepatic parenchymal disease and elderly. Minor increases in creatine-kinase (CK) activity in plasma have been observed. Rarely patient may have marked elevation in CK activity with generalized discomfort or skeletal muscle weakness. [2]

It's a fast changing world of glaring contrasts where development and environmental degradation, overfeeding and starvation, occurrence of infectious and life style diseases, takes place side by side. The modern medicinal system too, is not exception, curing on one hand and causing sickness through side effects on the other hand. Heartrendingly, the jolted human discretion has started taking stock of the situation turning to the natural and the indigenous. [15] Ayurveda, the ancient Indian system of medicine is abound with information regarding plant parts and products having medicinal properties lacking side effects. Arjuna tree's various parts, especially the bark, occupy the pride of place in the context of such medicinal values. [15] Terminalia arjuna (Family: Combretaceae) is a large, evergreen tree found throughout the greater part of Indian Peninsula. Bark of T.arjuna is a popular ingredient of many ayurvedic formulations used in the treatment of heart ailments. Though many reports are available on the efficacy of T.arjuna bark extract in hyperlipidemic states, presence of the same activity in its leave was not extensively reported. [16]

T.arjuna has been known to possess cardiovascular benefits as early as 500 BC and its bark has been used in Indian traditional system of medicine for over three centuries as a cardiotonic. Active constituents of Terminalia bark include tannins, cardenolide, triterpenoid saponins (arjunic acid, arjunolic acid, arjungenin and arjunglycosides), flavonoids (arjunone, arjunolone and luteolin), gallic acid, ellagic acid, oligomericproanthocyanidins, phytosterols and various minerals such as calcium, magnesium, zinc and copper. [17] The stem bark of T.arjuna is used by the Ayurvedic physicians in India for the treatment of various CVDs, collectively referred to as hritroga (in vernacular). It has been extensively studied in animal models, to demonstrate cardio-protective properties, ranging from positive inotropic, hypolipidemic, coronary vasodilatory and antioxidant effects to induction of stress protein in heart. [18] T. arjuna tree bark powder has significant antioxidant action. In addition, it has also been reported to have hypocholesterolaemic effect. [19] Myocardial fibrosis and oxidative stress accompany a number of cardiac disorders such as hypertrophic cardiomyopathy, hypertensive heart disease and cardiac failure. Stem bark of T. arjuna has been advocated for cardiac ailments. It protects against myocardial changes induced by chronic beta-adrenoceptor stimulation. [20] It has been reported that T.arjuna extract can effectively prevent the progress of atherosclerosis. This is likely due to the effect of T.arjuna on serum lipoproteins and its antioxidant and anti-inflammatory properties. [21] The hypocholesterolaemic effect of fraction of T. arjuna may be due to interference with the absorption of dietary cholesterol as well as bile acid from the intestine, increased elimination of the faecal sterols and increased stimulation of bile acid synthesis may lead to increased utilization of cellular free cholesterol. [22] Prolonged administration of T. arjuna did not show any adverse effects on renal, hepatic and hematological parameters.[23]

Treatment of dyslipidemia is central when aiming the long term relief

from angina, reduced need for revascularization and reduction in myocardial infarction and death. [8] In light of hypolipidemic, antianginal, anti-inflammatory and antioxidant activity of T.arjuna, these activities should be checked in comparison to the commonly used drugs i.e. statins for dyslipidemia. Statins are used since 1970s but are costlier and are having few side effects like myopathy and hepatic dysfunction. Limited number of studies had been done for hypolipidemic effect on T.arjuna, so we planned to evaluate the hypolipidemic effect in comparison to Rosuvastatin.

Material and methods

The present study was conducted by pharmacology department in association with department of medicine of Government Medical College and Rajindra Hospital, Patiala and was designed to evaluate and compare the hypolipidemic efficacy of Terminalia arjuna with Rosuvastatin in patients of dyslipidemia considering the previous reports of efficacy of T.arjuna. 60 patients of dyslipidemia coming to outdoor department of medicine were enrolled. The cases were selected on the basis of following criteria:-

Inclusion criteria

Age >20 years and patients with dyslipidemia, having: TC ≥ 200 mg/dl, LDL-C ≥ 130 mg/dl

Exclusion criteria

Pregnant women, patients with hepatic or renal failure, patients with rheumatic valvular lesion, patients having congenital heart disease and patients having history of epilepsy.

An open prospective randomized study was conducted for duration of 12 weeks in 60 patients of dyslipidemia. The patients fulfilling the inclusion criteria and have none of the exclusion criteria were included after taking written informed consent. This study was conducted with the permission of institutional ethical committee and all study procedures were performed according to the declaration of Helsinki. A detailed history of all patients was obtained and recorded. The complete clinical examination was done. TC and LDL-C levels of all patients were done at baseline. Then, these patients were distributed into two groups of 30 each by using stratified randomization technique. Patients of two groups were advised to follow lifestyle modification like regular exercise, quit smoking, have low fat diet and avoid alcohol intake. Group I- patients were started on Statin i.e. Rosuvastatin 10 mg once daily at bed time. Group II- patients were started on capsules containing bark powder of Terminalia arjuna 500 mg twice daily.

Patients were evaluated at 4, 8, and 12 weeks for TC and LDL-C levels. TC was analyzed by in vitro enzymatic colorimetric method described by Allian et al. LDL-C was determined by formula devised by Friedewald et al. Patients were advised to report immediately and stop the drug if he/she feels any undesirable symptoms during the treatment. The TC and LDL-C levels along with any undesirable effects were observed at the end of 12 weeks of treatment. These observations were compared with baseline values within the group and also between both the groups, and then evaluated. The results of observation of individual patients were pooled for each group. Data was expressed as mean ± standard deviation (SD). For statistical analysis of baseline characteristics i.e. gender, past and personal history chi-square test ($\chi 2$) was used and for age group student 't' was used. For TC and LDL-C parameters student 't' test was used. Paired 't' test was used for intra-

group comparison, evaluating the effect of treatment by comparing the values at 4, 8 and 12 weeks with the baseline values. Unpaired 't' test was used for inter-group comparison, for evaluating the effect of both the drugs. P value of less than 0.05 was considered as statistically significant.

Results

Baseline comparison

According to gender: In group I, 17 (56.67%) males and 13 (43.33%) females were included. In group II, 16 (53.33%) males and 14 (46.67%) females were included. This difference was statistically non-significant (p> 0.05)

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Past history: In group I past history of CAD, Hypertension and Diabetes mellitus were present in 7, 20 and 7 patients respectively, while absent in 23, 10 and 23 patients respectively. In group II past history of CAD, Hypertension and Diabetes mellitus were present in 7, 17 and 8 patients respectively, while absent in 23, 13 and 22 patients respectively (p> 0.05) .

Personal history: In group I, no patient had history of smoking, 4 patients were alcoholics and 20 patients had sedentary lifestyle. While in group II, 1 patient was smoker, 3 patients were alcoholics and 23 patients had sedentary lifestyle. The difference of personal history between group I and II was non-significant, so both the groups were comparable (p>0.05). As evident from table no.1, Baseline comparison for all parameters between the two groups has also shown no significant difference (p value >0.05). Therefore, both the groups were comparable at baseline.

The mean baseline total cholesterol ± standard deviation was 255.40 ± 30.31. All patients receiving Rosuvastatin treatment showed decrease in total cholesterol level from 255.40 ± 30.31 to 190.13±19.17 after 12 weeks of treatment. This difference was statistically highly significant. The mean baseline total cholesterol ± standard deviation was 253.40±29.26. All patients receiving T.arjuna treatment showed decrease in total cholesterol level from 253.40±29.26 to 181.47±22.40 after 12 weeks of treatment. This difference was statistically highly significant. As evident from table: 2 patients receiving Rosuvastatin treatment showed a decrease of 10.10%, 19.42% and 24.74% in total cholesterol level after 4, 8 and 12 weeks respectively. The patients receiving T.arjuna treatment showed a decrease of 14.06%, 24.73% and 27.89% in total cholesterol level after 4, 8 and 12 weeks respectively. The decrease was more in patients receiving T.arjuna, but on comparing the difference was statistically non-significant. (Fig.1)

The mean baseline low density lipoprotein cholesterol ± standard deviation was 159.67±22.06. All patients receiving Rosuvastatin treatment showed decrease in LDL-C level from 159.67±22.06 to 126.87±17.74 after 12 weeks of treatment. This difference was statistically highly significant. The mean baseline low density lipoprotein cholesterol ± standard deviation was 149.47±35.00. All patients receiving T.arjuna treatment showed decrease in LDL-C level from 149.47±35.00 to 114.40±31.30 after 12 weeks of treatment. This difference was statistically highly significant. Patients receiving Rosuvastatin treatment showed a decrease of 9.48%, 16.02% and 19.93% in LDL-C level after 4, 8 and 12 weeks respectively. The patients receiving T.arjuna treatment showed a decrease of 11.25%, 19.73% and 23.15% in LDL-C level after 4, 8 and 12 weeks respectively. The decrease was more in patients receiving T.arjuna, but on comparing the difference was statistically non-significant. (Table: 3, Fig.2)

Table: 1 Baseline characteristics of patients of group I (Rosuvastatin) and group II (T. arjuna)

Characteristics		Rosuvastatin (n=30)	T.arjuna (n=30)
Gender	Male	17 (56.67%)	16 (53.33%)
	Female	13 (43.33%)	14 (46.67%)
Age in years	Mean ± SD	57.37 ± 8.31	54.87 ± 7.33
Past history	CAD	7 (23.33%)	7 (23.33%)
	HTN	20 (66.67%)	17 (56.67%)
	DM	7 (23.33%)	8 (26.67%)
Personal history	Smoking	-	1 (3.33%)
	Alcohol	4 (13.33%)	3 (10%)
	Sedentary life style	20 (66.67%)	23 (76.67%)
Lipid profile	TC	255.40± 30.31	253.40±29.26
	LDL-C	159.67± 22.06	149.47 ± 35.00

Table: 2 Comparison of percentage change in mean total cholesterol (TC) level between group I (Rosuvastatin) and group II (T. arjuna) patients at different time interval

Time interval	Group	Mean ± SD	Mean change ± SD	%age Change
Baseline	I	255.40±30.31	-	-
	II	253.40±29.26	-	-
After 4 weeks	I	228.70±22.65	-26.70±15.84	-10.10
	II	216.93±26.28	-36.46±22.91	-14.06
After 8 weeks	I	203.97±22.30	-51.43±30.26	-19.42
	II	189.40±25.61	-64.00±30.80	-24.73
After 12 weeks	I	190.13±19.17	-65.26±31.80	-24.74
	II	181.47±22.40	-71.93±28.07	-27.89

(p value >0.05=Non Significant)

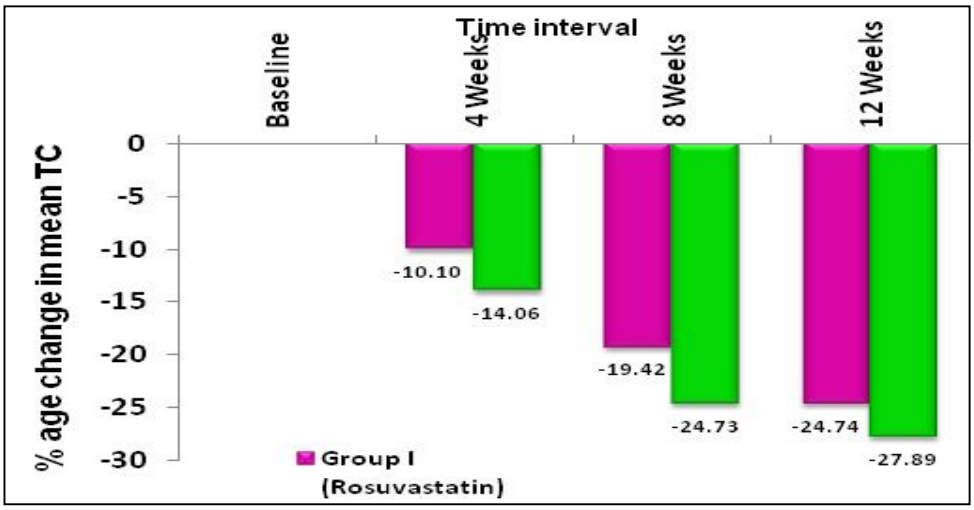

Fig.1 Percentage change in mean total cholesterol

Table: 3 Comparison of percentage change in mean low density lipoprotein cholesterol (LDL-C) level between group I (Rosuvastatin) and group II (T. arjuna) patients at different time interval

Time interval	Group	Mean ± SD	Mean change ± SD	%age change
Baseline	I	159.67±22.06	-	-
	II	149.47±35.00	-	-
After 4 weeks	I	144.10±18.82	-15.57±10.57	-9.48
	II	132.20±33.29	-17.27±18.76	-11.25
After 8 weeks	I	133.27±19.10	-26.40±17.61	-16.02
	II	119.83±33.49	-29.63±23.07	-19.73
After 12 weeks	I	126.87±17.74	-32.80±19.07	-19.93
	II	114.40±31.30	-35.07±23.41	-23.15

(p value >0.05=Non Significant)

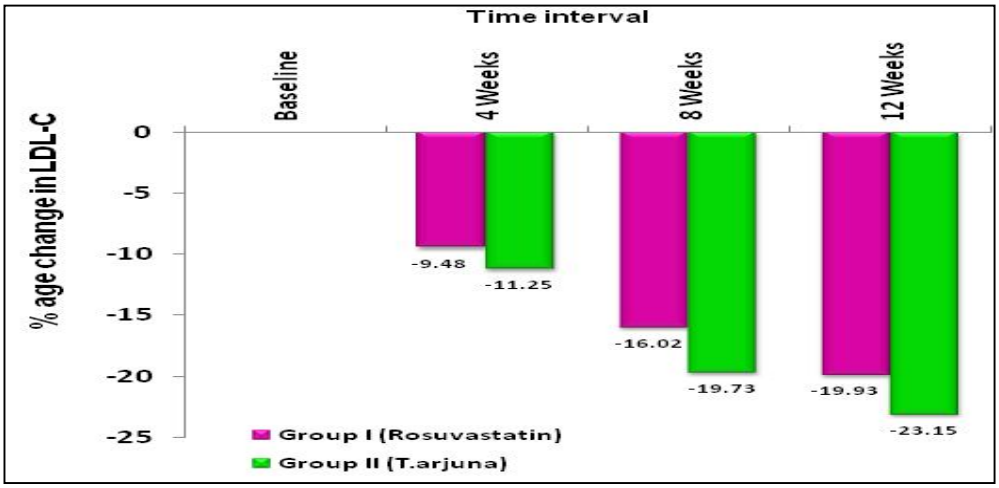

Fig.2 Percentage change in LDL cholesterol

Discussion

Dyslipidemia refers to elevation of plasma cholesterol, triglycerides (TGs), low-density lipoprotein (LDL) or a low level of high-density lipoprotein (HDL) that contributes to the development of atherosclerosis, a precursor for ischemic heart disease. [24] Statins are widely used to treat dyslipidemia. Unfortunately, these drugs have side effects. Hence, much attention has been focused on the use of natural products that have very few side effects. In present one such plant is Terminalia arjuna, used having hypocholesterolemic activities.[21]

The present study was designed to evaluate and compare the hypolipidemic efficacy of Terminalia arjuna with Rosuvastatin in patients of dyslipidemia considering the previous reports of efficacy of T.arjuna. The results revealed that both the drug (T.arjuna and Rosuvastatin) significantly reduces the LDL‑C and TC. In the present study, in group I (Rosuvastatin) significant reduction were observed in mean TC level (10.10%)(p<0.001), (19.42%)(p<0.001) and (24.74%)(p<0.001), and mean LDL-C level (9.48%)(p<0.001), (16.02%)(p<0.001) and (19.93%)(p<0.001) at the end of 4, 8 and 12 weeks of treatment respectively. In group II (T.arjuna) also significant reduction were observed in mean TC level (14.06)(p<0.001), (24.73%)(p<0.001) and (27.89%)(p<0.001), and mean LDL-C level (11.25%)(p<0.001), (19.73%)(p<0.001) and (23.15%)(p<0.001) at the end of 4, 8 and 12 weeks of treatment respectively. On analysing the data, it was found that group II (T.arjuna) lead to greater reduction than group I (Rosuvastatin) in mean TC level (14.06% vs 10.10%), (24.73% vs 19.42%) and (27.89% vs 24.74%) at 4, 8 and 12 weeks respectively. The reduction in mean LDL-C level was also greater with T.arjuna as compared to Rosuvastatin (11.25% vs 9.48%), (19.73% vs 16.02%) and (23.15% vs 19.93%) at 4, 8 and 12 weeks respectively.

Maulik and Katiyar [18] in a randomised placebo-controlled trial with 105 patients of coronary heart disease, received T.arjuna bark-powder (500 mg daily) for 30 days. There was a significant decrease in total cholesterol and LDL cholesterol levels. This is in accordance to the present study. Gupta et al [19] in a clinical trial of 30 days duration, compared the hypocholesterolemic effects of 500 mg per day T.arjuna tree bark powder with placebo. They found that there was a significant decrease in total cholesterol level (-9.7 ± 12.7%)(p<0.001) and LDL-C level (-15.8 ± 25.6%) (p<0.001). The better results in the present study may be due to longer study duration and higher dose of T.arjuna used. Kumar et al[25] in a clinical trial of 3 weeks, evaluated the efficacy of T.arjuna bark powder in dyslipidemic patients. The dose used was 5 gm per day and it was found that there was a significant reduction in the serum levels of TC and LDL-C (p<0.01). The percentage decrease in the levels of serum TC and LDL-C were 9.8% and 8.8% respectively. The better results in the present study may be due to longer study duration. Subramaniam et al [21] conducted a study in rabbits fed with high fat diet to determine the effect of T.arjuna on blood lipids and compared with effect of Atorvastatin. Atorvastatin points out significantly lowered levels of TC to 49.91, 51.16 and 55.70% (p<*0*.05). When treated with EtOH T.arjuna in 100 mg kg−1 of dose, the total cholesterol was reduced to the levels of 14.27, 27.61 and 30.36% of those of the HFD group (p<0.05). Treated group of EtOH fraction in 200 mg kg−1, the TC level was found to have of reduction to 24.16, 37.91 and 44.41% (*p<0*.05). Significant reductions in LDL-C

were found in Atorvastatin and T.arjuna treated groups ($p<0.05$). The hypolipidemic effect of T.arjuna was in accordance with the present study. Tiwari et al[26] in an experimental trial reported that hypercholesterolemic rabbits receiving T.arjuna treatment showed a more marked reduction in total cholesterol ($p<0.02$) than the hypercholesterolemic control rabbits. The hypolipidemic effect of T.arjuna was in accordance with the present study. Nissen et al[27] in a clinical trial of 24 months duration, found that with Rosuvastatin 40 mg per day, there was a mean reduction of 53.2% ($p<0.001$) in LDL-C levels. The present study is not with accordance, there was a mean reduction of 19.93% ($p<0.001$) in LDL-C levels , the better results in the study by Nissen et al may be due to longer duration of study with higher dose of Rosuvastatin as compare to our study.

Terminalia arjuna had a slight edge over Rosuvastatin as it showed greater reduction in total cholesterol and low density lipoprotein cholesterol levels. It was thus concluded from the present study that Terminalia arjuna was found to be well efficacious in dyslipidemic patients. The present study confirms the efficacy of T.arjuna as an effective hypoloipidemic agent. The factors responsible for lipid lowering effect of T.arjuna are still to be determined completely. But this conclusion is limited by the smaller sample size and short duration of study. Therefore further studies are needed to be conducted in large number of patients of dyslipidemia related disorders to confirm the therapeutic benefits of Terminalia arjuna.

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