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Original Article

A Study of the Safety and Efficacy of Alternate Day vs. Daily Rosuvastatin Dosing in Hypercholesterolemia Patients at Tertiary Care Hospital

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Abstract

Background
Many of the patients with coronary heart disease require lifelong statin administration. Patients usually discontinue the medicine either due to side effects like myalgia, hepatotoxicity or due to the cost of the medicine. The aim of this study is to see the scope of adjustment of the regimen to alternate-day dosing as an option to be considered in patients for whom adverse effects or cost are issues.

Materials and Methods
A comparative, prospective, parallel group and open study was performed on forty- two patients of both genders with dyslipidaemia within the age group of 30 to 60 years attending the out – patients department of Medicine of Nobel Medical College and Teaching Hospital from February 2020 to March 2020. Mean reductions in different lipid fractions in the two treatment groups over the eight-week study period was calculated and then compared. Frequencies of patients developing different side effects was also calculated and compared between the two groups.

Results
Baseline characters of both the groups were well balanced. Low density lipoprorein-C was reduced by 33.8 % in once-daily group and 31.3 % in alternate-day group, respectively. Changes were also recorded for the other lipid parameters. Such changes were found to be of no significant difference when compared between the two groups (p>0.05)

Conclusion
An alternate-day regimen of statin in patients of hyperlipidaemia showed similar effect on the lipid panel compared to daily regimen.

Key words: *Coronary Heart Disease, Hyperlipidaemia, Statins, low density lipoprotein cholesterol.*

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Introduction

Coronary heart disease (CHD) is the most common contributor of morbidity and mortality in underdeveloped and developing countries. Non-modifiable risk factors for coronary heart disease are advanced age, hereditary, gender, ethnicity and race while the modifiable risk factors are high blood pressure,dyslipidaemia, diabetes mellitus, physical inactivity, unhealthy diets [1]. Dyslipidaemia is an important risk factor for coronary artery disease [2]. Hyperlipidaemia or Dyslipidaemia; one of the many modifiable risk factors; is defined as elevated total cholesterol or LDL cholesterol levels, or low levels of HDL cholesterol. Statins, nicotinic acid, fibric acid derivatives, bile acid binding resins, inhibitors of intestinal cholesterol absorption are the drugs available for the treatment of dyslipidaemia- Statins are most commonly used drugs which act by inhibiting a key enzyme HMG CoAreductase involved in synthesis of cholesterol. Statins are the most effective agents at reducing LDL-C levels, as well as the occurrence of atherosclerotic events and cardiovascular morbidity and mortality. Additionally, statins have been shown to improve endothelial function, stabilize atherosclerotic plaques, decrease oxidative stress and inflammation, inhibit thrombogenic response, and reduce C-reactive protein (CRP) levels [3]. Many of the patients with the cardiovascular disease require lifelong statin administration. They usually discontinue the medicine either due to the side effects of the drug or due to costs of the medicine. Adverse effects such as myalgias, hepatotoxicity, gastrointestinal disturbances, and headache are among the more common adverse effects of statins, with myalgias occurring in up to 10% of patients [4]. Both myalgias and hepatotoxicity are considered to be dose related; therefore, reducing the systemic drug concentration may lower the incidence of these adverse drug reactions and increase adherence to the statin regimen. Presently available statins are Lovastatin, Simvastatin Pravastatin, Fluvastatin, Atorvastatin, Rosuvastatin. Plasma half-life of Rosuvastatin is high (18 to 24 hours) and causes greater rise of HDL cholesterol than other statins [5]. Given the relatively long half-lives of newerstatins, adjustment of the regimen to alternate-day dosing is an option to consider in patients for whom adverse effects or cost are issues. The present study was designed to study the efficacy and safety of the alternate day dosing of the Rosuvastatin versus daily dosing. Alternate day dosing of Rosuvastatin would help in reducing the cost and side effects in these individuals. There are similar studies conducted in other different countries and in different parts of Nepal. The present study was conducted in eastern region population among the patients attending the medicine OPD of Nobel Medical College and Teaching Hospital, Biratnagar.

Materials and Methods

The present study was a comparative eight - weeks, prospective, parallel group, open study performed on forty -two patients of both genders with dyslipidaemia within the age group of 30 to 60 years attending the out- patients department of Medicine of Nobel Medical College and Teaching Hospital. The study was conducted from February 2020 to March 2020 after being approved by the Institutional Review Committee. A written informed consent was taken from all the patients included in this study. The study considers 95% confidence interval and 80% power to evaluate the sample size. Since all the samples were a diagnosed case of hypercholesterolaemia and according to the literature review prevalence of mixed dyslipidaemia is 88 % amongst them. Now using the formula, $n = z^2 p q/l^2$ where Z= 1.96 at 95% confidence interval, p =88%, q=12% and l=20% of p i.e.; 18. Putting in the formula n= 13. But 21 cases in each group were included to compensate any dropouts. Patients diagnosed with hypercholesterolaemia were screened by physicians and was referred to the investigators for subject eligibility assessment. Eligibility was determined by baseline laboratory data Total cholesterol > 200mg/dl, HDL-C < 40mg/dl for men &< 50mg/dl for women, LDL > 130mg/dl and TGs > 150mg/dl. Patient with history of allergy to statins, receiving any hypolipidemic agent (e.g., in MI, Stroke) by the time of the tests, alcohol intake, chronic hepatitis, asthma or chronic obstructive pulmonary disease, pregnancy, lactating females, unexplained increase in creatinine kinase to >3 times the upper limit of normal and abnormal levels of aminotransferases were not included in the study. Patients were excluded if they were taking drugs known to affect lipid metabolism or to interact with rosuvastatin (e.g., oestrogen, corticosteroids). Other exclusion criteria included unwillingness of the patient and presence of any underlying condition producing dyslipidaemia including hypothyroidism, nephrotic syndrome, biliary obstruction, and renal failure. Written informed consent was collected from all eligible patients in their native language. Eligible patients were randomly divided into groups A and B

following odd-even method. Group A was treated with daily dose10 mg of a particular brand of rosuvastatin (odd no. patients) and group B was treated with alternate day 10 mg of the same brand of rosuvastatin (even no. patients) for eight weeks. Patients were advised to take it regularly after dinner and before bed time. 12 hour fasting blood samples were obtained to evaluate lipid levels and safety parameters like LFT, creatinine kinase, serum creatinine before initiating the therapy. A low cholesterol containing diet was prescribed to both the groups before initiating the therapy. Patients were counselled about the probable adverse effects of rosuvastatin including those on the hepatic and musculoskeletal system. The participants were asked to contact us if he/she experiences any muscle pain/cramps, malaise, pale stool or dark urine. Fasting plasma lipid profile was measured on 0 day, on the completion of 4th and 8th week and serums ALT, AST was estimated in both the groups on 0 day and 8th week. Patients was phoned by the investigators at the completion of 4 weeks for recording any adverse event, Safety and tolerability was evaluated throughout the study on the basis of adverse events, patient interviews, physical examinations, and laboratory studies (i.e., serum AST, ALT,). All laboratory samples were obtained at random between 9:00 and 11:00am.

SPSS was used for data analysis. All quantitative variables were described as mean ± standard deviation. Mean reductions in different lipid fractions in the two treatment groups over the eight-week study period was calculated and then compared using independent samples t-test. *p* value of ≤0.05will was considered significant.

Results

A total of 42 patients participated in the study and consist of 15 females (36%) and 27 males (64%). All the patients belonged to lower and middle socio-economic status. Distribution of patients in the age group of 31-40 years were 36%; 41-50 years were 38% and 51-60 years were 26%. There was no significant difference in baseline parameters of lipid profile between the two groups. *(p>0.05)* (Table 1)

The results of the study demonstrated that the lipid levels varied from zero to 8 th week in each test group significantly but they did not vary much when compared between the two test groups showing both the therapies are similar in efficacy (Table 2 and Table 3).

Table 1: Mean of the lipid panel of patients with dyslipidaemia receiving daily dosing rosuvastatin (n = 21) Group A and alternate day dosing of rosuvastatin (n = 21) Group B before initiation of therapy at 0 day

Baseline characteristics	Group A (daily dosing)	Group B (alternate day dosing)	P
Number of patients	21	21	
Age range (in years)	30-60	30-60	
Sex (male/female)	14/7	13/8	
TC (mg/dl)	256.57±40.21	236.91±22.84	NS *(p>0.05)*
LDL	180.35±33.29	162.32±17.67	NS *(p>0.05)*
HDL	42.17±6.49	42.95±7.01	NS *(p>0.05)*
TG	212.17±69.00	222.00±77.54	NS *(p>0.05)*

Table 2: Changes in the lipid profile in the daily rosuvastatin, group - A and alternate day rosuvastatin group - B (Mean±SD) and student paired t test

Parameter	Groups	At 0 weeks	At 4 weeks	At 8 weeks	P value 0 weeks versus 8 wks
TC	Group A	256.57±40.21	220±29.61	194.53±22.56	P< 0.0001
	Group B	236.91±22.84	209.55±15.55	185.29±12.58	P< 0.0001
LDL	Group A	180.35±33.29	148.43±28.21	119.32±21.07	P< 0.0001
	Group B	162.32±17.67	135.27±13.43	111.38±10.62	P< 0.0001
HDL	Group A	42.17±6.49	45.43±7.26	50.16±6.84	P<0.0001
	Group B	42.95±7.01	45.41±6.56	49.95±6.26	P< 0.0001
Triglycerides	Group A	212.17±69	152.44±37.98	133.58±27.91	P< 0.0001
	Group B	222.00±77.54	151.50±40.73	129.43±26.32	P< 0.0001

Table 3: Inter group comparison of Lipid Profile at Baseline and at 8 week

Parameter (mg%)	Mean ± SD Baseline Group A	Group B	'p'	Mean ± SD At 8 Weeks Group A	Group B	'p'
TC	256.57±40.2	236.91±22.84	>0.05	194.53±22.56	185.29±12.58	>0.05
TG	212.17±69	222.00±77.54	>0.05	133.58±27.91	129.43±26.32	>0.05
LDL	180.35±33.2	162.32±17.67	>0.05	119.32±21.07	111.38±10.62	>0.05
HDL	42.17±6.49	42.95±7.01	>0.05	50.16±6.84	49.95±6.26	>0.05

The reduction in total cholesterol was highly significant in group A (daily) and group B (alternate day) at the end of 8 th week of therapy, showing percentage of reduction as 24.2% versus 21.7% respectively. The difference in percentage is 2.5%. Similarly, the reduction in LDL-C was also highly significant in group A (daily) and group B (alternate day) at the end of 8

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th week showing percentage reduction as 33.8% and 31.3% respectively. The difference in the percentage is 2.5%. Rosuvastatin was well tolerated over eight week's durations; the main adverse events that were experienced by the patients in either group were that of gastrointestinal symptoms (nausea, diarrhoea and constipation) and headache which were within tolerable limits. No patient discontinued the study during the study period due to the adverse effect. The estimation of liver enzymes-serum ALT, AST at end of 8 th week in group A and group B have shown that there is no significant rise in the levels and were within normal limits (Table 4).

Table 4: Inter group comparison of Lipid Profile at Baseline and at 8 weeks

	Timeline	Group-A	Group-B	P value
ALT	Baseline	28.42±1.302	27.97±1.180	0.7997(NS)
	8 th week	28.42±1.312	27.89±1.190	0.7672(NS)
AST	Baseline	32.82±1.278	31.68±1.313	0.5386(NS)
	8 th week	32.29±1.311	32.085±1.218	0.8951(NS)

Discussion

LDL-C is a well-established risk factor for cardiovascular disease, and there is considerable evidence that lowering LDL-C reduces the risk of both cardiovascular events and mortality [6-7]. The real clinical benefits of statins are due to their LDL-C lowering effects and this benefit has been observed in clinical trials. Rosuvastatin has been approved for use at doses of 5 – 40 mg to reduce LDL-C and improve HDL and other parameters in dyslipidaemic patients. Rosuvastatin was chosen to perform the present study because Rosuvastatin is a suitable drug for alternate-day application due to longer half-lives (18–20 h) [5]. Their prolonged survival and HMG-CoA reductase inhibition allows Rosuvastatin to be dosed every other day, but this possibility is unknown to many clinicians [8]. The present study of 8 weeks duration has achieved percentage decrease in LDL-C 33.8% in daily regimen and 31.3% in alternate day regimen. The difference in reduction of percentage was 2.5%. It shows alternate day regimen is similar in efficacy and also attained nearly the same percentage of reduction in 8 weeks duration. According to the previous study done by Wongwiwatthananukit S et al the reduction of LDL-C in once daily regimen was 48% and 39% reduction was seen in alternate regimen after 8 weeks. The difference in reduction of percentage was 9% [9]. The differences in reduction of percentage compared to the previous study could be due to the differences in

culture, socioeconomic background, lifestyle and food habits of the participants enrolled in the study. When we compare the daily day therapy with every other day therapy of 10mg Rosuvastatin, there was no significant difference in the LDL –C lowering capability with the use of either regimen. There was a similar percent reduction of LDL-C with the use of either therapy. This demonstrates that both the therapies are equally efficacious in providing improvement in the LDL-C in dyslipidemic patients. In a study conducted by Li et al [10], no significant difference in the decrease in LDL-C was observed with daily dosing when compared to alternate day dosing of 10 mg Rosuvastatin for eight weeks

There is highly significant reduction in all the lipid parameters like total cholesterol, LDL-C, triglycerides and highly significant raise in HDL levels after eight weeks of the treatment period in both group A and group B showing p value <0. 0001. When compared between the two groups the alternate day therapy of rosuvastatin 10 mg is similar in efficacy compared to daily dose of rosuvastatin. The study also has achieved more reduction in triglyceride levels in group B than group A. Hypertriglyceridemia when associated with high LDL-C significantly increases the risk of coronary heart disease. In this study alternate day dosing reduced more TG levels than daily dosing. Hence it is highly beneficial and could be a better option for patients with hypertriglyceridemia.

In Nepal therapy with rosuvastatin in usual recommended dose may cost between Rs. 600 - Rs. 1000 per month. The lower- and middle-income groups of Nepalese society are suffering the economic burden of rosuvastatin therapy. Rosuvastatin being a drug with long half-life, this study proposes that by using alternate day doses of rosuvastatin a significant LDL-C reduction, increase in HDL levels and more reduction in TG levels may still be achieved while reducing the total cost of treatment [11]. ADR`s with rosuvastatin are minimal compared to the other statins [12]. By choosing alternate day regimen, not only there is reduction in cost, the ADR`s with rosuvastatin are sub minimized compared to daily regimen.

Conclusion

An alternate-day regimen of statin in patients of hyperlipidaemia showed similar effect on the lipid panel compared to daily regimen and maybe useful in decreasing the cost of therapy and minimizing the adverse effects.

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Conflicts of interests: None

References

[1] Gupta S, Ramesh Gudapati KG, Bhise M, Emerging risk factors for cardiovascular diseases: Indian context. Indian journal of endocrinology and metabolism. 17:5 (2013) 806. DOI: 10.4103/2230-8210. 117212.

[2] Fodor G, Primary prevention of CVD: treating dyslipidemia. American Family Physician, 83:10 (2011) 1207. PMID: 21418693.

[3] Grundy SM, Cleeman JI, Merz CNB, et al, Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 13 (2004) 227-39. DOI 10.1161/01. CIR.0000133317.49796.0E

[4] Mitka M, Expanding statin use to help more at-risk patients is causing financial heartburn. Jama. 290:17 (2003) 2243-5. DOI 10.1001/jama.290.17.22

[5] Bertam.G, Katzung, Susan B Masters, Anthony J Trevor, Basic and clinical pharmacology:Agents used in dyslipidemia. 11thedition.New York: Mc Graw hill lange publication, 2009. pg 605.

[6] Li JJ, Lu ZL, Kou WR, Chen Z, Wu YF, Yu XH, et al, Impact of Xuezhikang on coronary events in hypertensive patients with previous myocardial infarction from China Coronary Secondary Prevention Study (CCS PS), Ann Med 42 (2010) 231-40. DOI: 10.1177/0091270009337509. PMID: 19602720

[7] Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult treatment Panel III). JAMA 285 (2001) 2486-97. DOI: 10.1001/jama.285. 19.2486. PMID: 11368702

[8] Mc Taggart F, Buckett L, Davidson R, Holdgate G, McCormick A, Schneck D, et al, Preclinical and Clinical Pharmacology of Rosuvastatin, a new 3-hydroxy-3-methyl glutaryl coenzyme A reductase inhibitor, Am J Cardiol 87:Suppl B (2001) 28-32B. DOI: 10.1016/s0002-9149(01)01454-0. PMID: 11256847

[9] Wongwiwatthananukit S, Sansanayudh N, Dhummauppakorn R, Kitiyadisai C, The efficacy and safety of rosuvastatin every other day compared with once daily in patient with hypercholesterolemia, The Annals of pharmacotherapy. 40:11 (2006) 1917-23 DOI: 10.1345/aph.1H124. PMID: 17003082

[10] Li JJ, Yang P, Liu J, Jia YJ, Li ZC, Guo YL et al, Impact of 10 mg rosuvastatin daily or alternate-day on lipid profile and inflammatory markers, Clinica Chimica Acta 413:1 (2012) 139- 42. DOI: 10.1016/j.cca.2011. 09.006. PMID: 21983163

[11] WHO collobaratingcentre for drug statistic and methodology. ATC classification index with DDDs; 2011. https://www.whocc.no/ (accessed on 12.04. 2021)

[12] Clearfield MB, Amerena J, Bassand JP, Hernández García HR, Miller SS, Sosef FF, et al, Comparison of efficacy and safety of rosuvastatin 10 mg and Atorvastatin 20 mg in high risk patients with hypercholesterolemia. Prospective study to evaluate the use of low doses of the statins atorvastatin and rosuvastatin (PULSAR), Trials. 7:35 (2006). DOI: 10.1186/1745-6215-7-35. PMID: 17184550

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