



A Study on Correlation of Peripheral Neuropathy in Patients Receiving Atorvastatin Therapy- A Study in North Bihar

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Abstract

The role of statins to reduce risks of vascular death, non fatal myocardial infarction and stroke, is well established. STATIN competitively inhibit enzyme HMG-CoA reductase which convert HMG-CoA to mevalonate. Atorvastatin the most popular statin is more potent and appears to have the highest LDL-CH lowering efficacy. There are several case reports of statin induced peripheral neuropathy. The aim of the study is to find a correlation of development of peripheral neuropathy in patients receiving atorvastatin.

Methods: *Patients (age >30years, both gender) attending outdoor clinic and indoor patients of Medicine department darbhanga medical college were selected by simple random method taking atorvastatin for different indications, dosages and duration. The statistical significance of development of peripheral neuropathy was measured.*

Results: *There was development of peripheral neuropathy in about 26% individuals receiving atorvastatin therapy. Seven males and six females developed neuropathy out of total 29 and 21 respectively. Out of total 50 individuals 20 was free from any co-morbidity. Only 2 out of 20 developed peripheral neuropathy. Patient having only diabetes as co-morbidity was 10 and out of that 3 developed peripheral neuropathy. Individual having both diabetes and dyslipidemia were 11 and among them 2 developed peripheral neuropathy. And patients having diabetes, dyslipidemia and hypertension was 9 and 6 developed neuropathy.*

Conclusion: *A substantial proportion of patients taking atorvastatin have peripheral neuropathy (26%).It was observed that neuropathy in patients taking statins does not depend on sex. Diabetes, dyslipidemia and hypertension as a co-morbidity increases the risk of neuropathy in atorvastatin users. Statin induced neuropathy or neuropathy where statin is the only implicating factor is less common than diabetic or other neuropathies.*

Introduction

Various pharmacologic agents are available for the treatment of hypercholesterolemia, including 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, commonly referred to as statins, which offer favourable lipid lowering effects and reductions in morbidity and mortality. The preventive effect of cholesterol lowering treatment with statins on the risk of coronary heart disease, stroke, and total mortality is well

reported. Their ability to reduce the risks of vascular death, non-fatal myocardial infarction, stroke, and the need for arterial revascularization procedures has been shown by several large, high-quality randomized trials. In these trials, the extent of risk reduction was judged to be directly proportional to the degree to which LDL (low-density lipoprotein) cholesterol was lowered consistent with this being the main mechanism. Besides their efficacy, HMG-CoA reductase

inhibitors can also produce a variety of adverse drug reactions. The most serious ADRs are musculoskeletal symptoms including myopathy and myositis and life threatening rhabdomyolysis and liver failure.

There are several case reports of statin induced peripheral neuropathy and several cross sectional studies have shown an association of statin use and the development of peripheral neuropathy. It is also stated by others that statins increase the risk of peripheral neuropathy in diabetics but it also increase the risk in non-diabetics.

The aim of the study is to explore a possible role of atorvastatin in development of peripheral neuropathy in diabetic, hypertensive and dyslipidemic individual as well as those free from such co-morbid conditions in population.

Methods

This was a prospective study of correlation of peripheral neuropathy in patients receiving atorvastatin therapy. The study was conducted over a period of six months (1st February to 31st July 2017) on patients attending outdoor and indoor clinic of darbhanga medical college and hospital (a government medical college of north Bihar).

The study population included patients of at least 30 years of age of both genders taking statins and not previously diagnosed as a case of peripheral neuropathy.

Seriously ill patients and patients having co morbid conditions other than diabetes and dyslipidemia and hypertension that can give rise to peripheral neuropathy were excluded from the study. Patients fulfilling criteria were included in the study after acquiring informed consent.

The primary objective of study was to find whether statin use and co-morbid conditions have any role in development of peripheral neuropathy. Patients enrolled were assessed and examined at regular intervals. A nerve conduction velocity (NCV) test was performed for assessing the development of peripheral neuropathy.

Sample size was 50 subjects. Chi square test was used to determine the statistical significance. A p value of <0.05 was considered statistical significant.

No ethical committee issues were raised during the study.

Result

A total number of 50 patients were selected randomly for inclusion in the study that fulfilled the inclusion criteria, out of whom 29(58%) were males and 21(42%) was females. Out of 50 patients 20 patients had no co-morbidity associated, while 10 had diabetes, 11 had diabetes with dyslipidemia and 9 had diabetes plus hypertension with dyslipidemia.

All the 50 patients underwent assessment for development of peripheral neuropathy and NCV test was done. 13 (26%) patients out of 50 developed peripheral neuropathy. But it was found that there is no relationship of sex with the development neuropathy. P value was 0.724 therefore it was statistically insignificant.

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
SEX1 * NCV2	50	100.0%	0	0.0%	50	100.0%

SEX1 * NCV2 Crosstabulation

			NCV2		Total
			ABSENT	PRESENT	
SEX1	MALE	Count	22	7	29
		Expected Count	21.5	7.5	29.0
	FEMALE	Count	15	6	21
		Expected Count	15.5	5.5	21.0
Total		Count	37	13	50
		Expected Count	37.0	13.0	50.0

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.124 ^a	1	.724		
Continuity Correction ^b	.001	1	.979		
Likelihood Ratio	.124	1	.725		
Fisher's Exact Test				.754	.486
N of Valid Cases	50				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 5.46.

b. Computed only for a 2x2 table

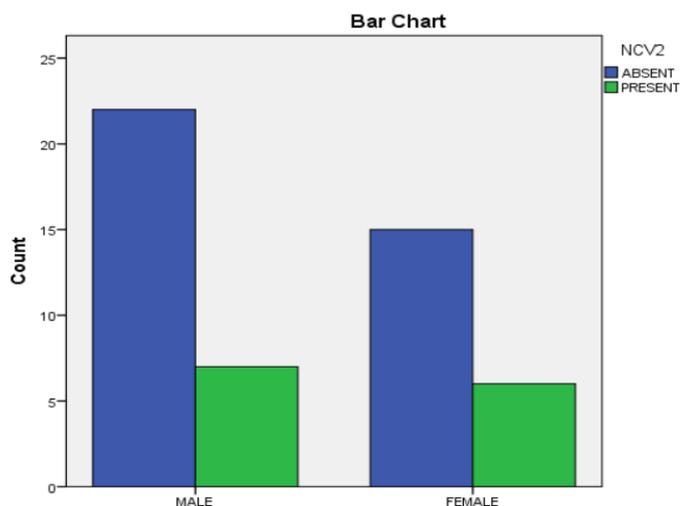


Fig. Bar chart showing development of neuropathy in males and females.

Out of total 50 patients, 20 Patients who had no co-morbid conditions only 2 developed neuropathy. Out of 10 diabetic patients 3 developed neuropathy. Individual having both diabetes and dyslipidemia were 11 and among them 2 developed peripheral neuropathy. And patients having diabetes, dyslipidemia and hypertension was 9 and 6 developed neuropathy. The development of peripheral neuropathy and co morbidities came to be statistically significant. The p value came to be 0.013.

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	10.830 ^a	3	.013
Likelihood Ratio	10.197	3	.017
Linear-by-Linear Association	7.270	1	.007
N of Valid Cases	50		

a. 3 cells (37.5%) have expected count less than 5. The minimum expected count is 2.34.

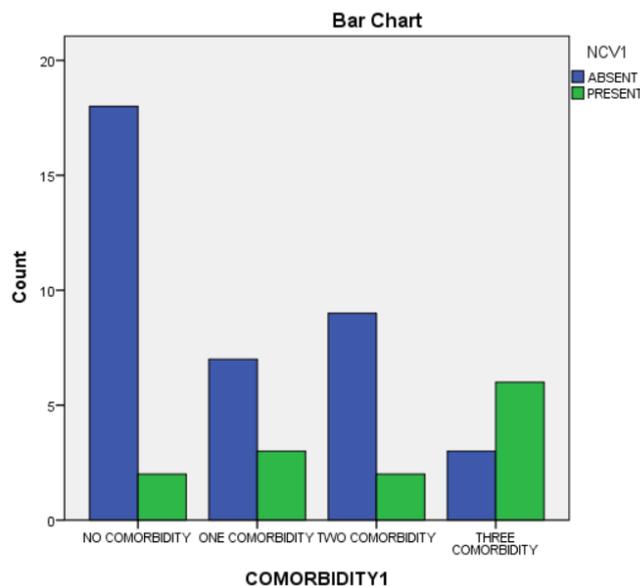


Fig. Bar chart showing development of neuropathy in individual having some co-morbid conditions.

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
COMORBIDITY1 * NCV1	50	100.0%	0	0.0%	50	100.0%

COMORBIDITY1 * NCV1 Crosstabulation

			NCV1		Total
			ABSENT	PRESENT	
COMORBIDITY1	NO COMORBIDITY	Count	18	2	20
		Expected Count	14.8	5.2	20.0
	ONE COMORBIDITY	Count	7	3	10
		Expected Count	7.4	2.6	10.0
	TWO COMORBIDITY	Count	9	2	11
		Expected Count	8.1	2.9	11.0
	THREE COMORBIDITY	Count	3	6	9
		Expected Count	6.7	2.3	9.0
Total		Count	37	13	50
		Expected Count	37.0	13.0	50.0

Discussion

Several lipid lowering agents are available as adjunctive therapy for the treatment of hyperlipidemia. Statins are effective lipid lowering agents that are widely prescribed (approximately 25 million patients receive them). These agents reduce cholesterol levels, particularly low density lipoprotein cholesterol (LDL), in patients with hyperlipidemia at risk for cardiovascular disease. In general, statin monotherapy is associated with few adverse effects, the most serious being hepatic and skeletal muscle toxicity. Clinically significant treatment related adverse effects are rare. Epidemiologic evidence suggests that the incidence of peripheral neuropathy due to statins is approximately 1 person/14000 person years of treatment.

Peripheral neuropathy is any disease process of one or more peripheral nerves. The causes of peripheral neuropathy are diverse and include certain drugs and toxins. Diagnostic of peripheral neuropathy often can be made from clinical setting (e.g. long standing diabetes mellitus); however proper history and physical examination should be performed to distinguish the origin as peripheral versus central and to ascertain involvement of muscle as well as the neuromuscular junction. Pain, most commonly due to axonal neuropathies, reflects involvement of small myelinated or unmyelinated fibers (type A or C). Sensory examination is important to determine the distribution and modalities involved. Diagnostic testing is used beyond the history and physical examination to distinguish between potential etiologies. It includes electro diagnostic testing, blood tests and in some cases, nerve biopsy. The peripheral neuropathies associated with drugs, toxins and metabolic disorders are typically polyneuropathies, affecting all nerves with a distal “stocking glove” pattern. Clinical features include muscle weakness, paresthesias and / or muscle weakness of lower extremities⁴⁰. The involved nerves may show mainly axonal degeneration (necrosis), principally segmental demyelination (loss of myelin from one or more internodes), or a mixture of both. The mechanism by which statins may cause peripheral neuropathy is not fully known. Whereas several mechanisms have been postulated, the most accepted theory pertains to these agents’ ability to inhibit HMG-CoA reductase. By inhibiting this enzyme, statins reduce not only the production of cholesterol but also the production of intermediates of farnesyl pyrophosphates, mainly ubiquinones. First, cellular membrane is composed of both lipid (compacted bi-layer) and protein. Marked reduction of cholesterol may alter membrane composition or function. It is possible that a less lipophilic state allows fewer protein interactions within the cellular membrane. Second, ubiquinone is an important enzyme in the mitochondrial respiratory chain). Because

cholesterol is a ubiquitous component of human cell membranes, interference with its synthesis may have many consequences. A deficiency or reduction in levels of ubiquinone can disturb energy use by the neuron(s).

This postulated mechanism may be responsible for axonal degeneration, which is common in neuropathies induced by drugs or toxins; such neuropathies are usually of the dying back type because the neuronal cell body and proximal axon remain intact, axonal regeneration and return of nerve function may be possible if the cause is identified and removed (e.g. discontinuation of statin). Electro physiologic studies suggest that the underlying pathology is most likely axonal degeneration of the large fiber type, with no features of demyelination. Irreversible structural and functional changes to neurons after long term statin exposure can be explained by both mechanisms. Elevated triglyceride levels (>400 but most often > 800 mg/dl) may be associated with a specific form of peripheral neuropathy, but clinicians should make this assumption only after other potential causes of neuropathy are excluded. In our study we found several important, statistically significant observations related to development of neuropathy. It is observed that neuropathy in patients taking statins does not depend on sex. There is no statistically significant difference between males and females regarding occurrence of neuropathy.

Therefore neuropathy in statin users is not dependent on sex or age but is strongly associated with presence of co-morbidities, particularly diabetes with or without dyslipidemia and hypertension. Diabetes, dyslipidemia or hypertension may individually cause neuropathy and are therefore strong confounding factors.

It is already known that statins by virtue of their pleiotropic effects stabilizes atherosclerotic plaques, prevents plaque rupture, restores vascular health and prevents major vascular events.

Further studies are required for a detailed understanding of the exact nature of nerve involvement with statin therapy. For example, if

motor or sensory nerves are preferentially involved and whether axonal or demyelinating neuropathy occurs as a result of statin therapy. There is ample scope of research regarding the blood levels of glucose and development of neuropathy as well as correlation between HbA_{1c} levels and neuropathy taking into consideration the usage of atorvastatin in these patients as a significant modifier.

Conclusion

HMG Co-A reductase inhibitors or statins are widely used for lipid lowering and other beneficial effects in cardiovascular diseases. Pleiotropic effects of statins are independent of their lipid lowering effects and have mortality benefit in cardiovascular diseases. These observations have caused increased use of these medications and in higher doses, particularly in acute coronary syndromes, in recent times. Thus, previously unrecognized side effects have become more and more apparent with passage of time, particularly if the side effect is slow to develop or takes a longer duration to manifest or if it is observed with a higher dose of statins as opposed to standard dose of statins.

A substantial proportion of patients taking atorvastatin have peripheral neuropathy (26%). Statin induced neuropathy or neuropathy where statin is the only implicating factor is less common than diabetic or other neuropathies.

A substantial proportion of patients with statin induced neuropathy may remain asymptomatic for a variable period of time and thus elude early diagnosis risking progression of disease gradually to an irreversible state.

Electrophysiological studies are sensitive and specific in detecting the appearance of neuropathy in earlier stages.

Diabetes, dyslipidemia and hypertension as a comorbidity increases the risk of neuropathy in atorvastatin users.

Clinicians should be aware that there is a potential risk of developing peripheral neuropathy for patients who take statins. Available data suggest

that the frequency of peripheral neuropathy is probably extremely low, considering the huge number of statin prescriptions filled worldwide. On the other hand, the rate at which peripheral neuropathy occurs may be underestimated. It is important to note that therapeutic applications of statin therapy are growing, so more cases or rare adverse effects may be reported. Patients taking statins should be questioned periodically about symptoms consistent with peripheral neuropathy. If peripheral neuropathy is suspected, a complete evaluation, including nerve conduction studies may be needed.

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