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ORIGINAL ARTICLE

HIGH INTENSITY STATIN IN ISCHEMIC STROKE: EXPERIENCE FROM A TERTIARY CARE HOSPITAL OF PESHAWAR, PAKISTAN

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ABSTRACT

Background: High intensity statins are one of the pillar of secondary stroke prevention. It has been a common practice to prescribe lower-than-recommended statin doses because of concerns regarding drug toxicity in Asians population. This necessitates investigation rather than assumption. Objective of this study was to determine the short term effect of high intensity statins in secondary prevention of stroke in terms of low density lipoprotein (LDL) reduction and frequency of myopathy.

Materials & Methods: A Prospective observational study was conducted in Rehman Medical Institute, Peshawar. patient diagnosed with ischemic stroke, were prescribed high intensity Atrovastatin and rusuvastatin. Baseline modified Rankin Scale along with Creatinine phosphate kinase (CPK), Thyroid stimulating hormone (TSH), Alanine transaminase (ALT) and renal profile were recorded. Patients followed up after 6weeks. On follow up symptoms and signs of myopathy along with serum CPK level were recorded. The patients having myopathy were categorized as per SRM classification.

Results: A total of 202 patients, 13 fail to follow up. Among the 189 patients included 59.8% (113) were males whereas (40.2%) 76 were females. The Mean LDL (low density lipoprotein) at admission was 121.43±21.56 mg/dL. Of all, 51.9% of the participants received 40 milligrams of atorvastatin. At 6 weeks follow-up The Mean Low density lipoprotein LDL level were 61.12 ± 27.29. mg/dl. No patient developed symptoms or muscle tenderness on examination. However, 4.2% (8) patients had raised CPK on follow-up and fell into Statin related myopathy (SRM) 0. None of the patients suffered from any other type of SRM.

Conclusions: A very limited percentage of the participants developed mild, asymptomatic myopathy (SRM0). None got any other class of SRM. There was no significant association of myopathy with age, gender, mRs, premorbids and type of statin used. With high intensity statin we managed to achieve desired LDL levels in a significant number of patient on 6 weeks follow up.

KEY WORDS: statin; atorvastatin; rosuvastatin; myopathy.

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1. INTRODUCTION

Stroke is the leading cause of mortality and morbidity worldwide. There is high risk of recurrent stroke after 1st episode of ischemic stroke or transient ischemic attack (TIA). This fact leads to the concept of an early and aggressive approach to secondary stroke prevention with antiplatelets and statins. This approach decreases the risk of subsequent stroke significantly.[1] The annual risk of recurrent ischemic stroke is 3 to 5%.[2] Patients who suffers ischemic stroke or TIA are also at high risk for subsequent atherosclerotic heart disease.[2] Current lipid guidelines strongly recommend statin therapy for secondary prevention of Ischemic stroke and Ischemic heart disease.[3,4] Despite the proven role of statins in preventing recurrent ischemic events, patients are often untreated or undertreated with lower-than-recommended dose of statins especially in our settings.[5-7]

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Unfortunately, the international guidelines are based on studies on western population mostly so the data efficacy and safety of high intensity statins in Asian population is deficient.[8] Asian ethnicity have higher risk of atherosclerotic vascular disease as compared to West.[9] Despite the compelling need and recommendation, High intensity statins are not being prescribed and used due to lack of evidence and concern of high risk of myopathy in Asian population.[10-13] Lower adherence rate with high intensity statin (0.4% and 1.9%) have been reported in two studies when compared to the patients using moderate intensity.[6,7] This practitioner and patients approach has been translated into high incidence of stroke and re stroke in Asia as compared to western world.[14,15] A meta-analysis comprises of 15 studies described that 45% increase in all-cause mortality and 15% increase in atherosclerotic events in patients taking lower doses of statin therapy versus higher doses.[16]

Clinical benefit of high versus low dose of a statin has been also documented in Asian population. REAL-CAD trial [Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease]) from Japan was breakthrough in this regard. High intensity statins reduced the all cause mortality significantly in Japenese population. More over, this trail also showed no evidence of serious side effects with higher doses.[17]

It has been postulized that Asian population is at high risk of developing statin induce myopathy however this has not been supported by any of the study from Southeast Asia in the settings of stroke prevention. For the said reason, majority population has been under treated. This necessitates investigation rather than assumption. This study was planned to access the safety of high intensity statins for secondary prevention of stroke in Pakistani population. This study will be pioneering work not only from Pakistan but also from Asia, focusing on objective evidence of high intensity statin induced myopathy in patients with ischemic stroke. Moreover we have also described the short term effect of high intensity statin therapy in Ischemic stroke. The implication of this study will be two folds; 1st it will identify the magnitude of myopathy related to high intensity statins in Asian population. Secondly, it will bring international guidelines into practice, thus reducing the recurrence of Ischemic stroke causing long-term morbidity and mortality.

1.1 Objectives:

To determine the effect of high intensity statins in secondary prevention of stroke. To describe frequency of myopathy and its associated factors in patients treated with high intensity statin therapy.

2. MATERIALS AND METHODS

This prospective observational study was conducted in Stroke Unit, Rehman Medical Institute, Peshawar, Pakistan from May 1, 2021 to April 30, 2022. The ethical approval was taken from Research Evaluation Cell, Rehman Medical College.

Patients diagnosed with acute Ischemic stroke aged above 18 years were included in study. Acute Ischemic stroke was defined according to the most recent definition of stroke for clinical trials. It requires either focal neurological deficit lasting >24 h or imaging of an acute clinically relevant brain lesion in patients with rapidly vanishing symptoms.[1] Patients with history of myopathy, thyroid dysfunction, renal and liver impairment and those on medication interacting with statin metabolism were excluded. More over baseline Creatine kinase (CPK), Thyroid stimulating hormone(TSH) was carried out if abnormal, patients were excluded. Sample size was calculated using Open EPI, taking anticipated frequency of statin induced myopathy as 15% [18], keeping 95% confidence level, sample size came out to be 185. Keeping the drop out rate , we recruited 202 patients in our study by consecutive nonprobability technique. Written informed consent was taken from all patients or their attendant where patient was unable to give consent.

All the patients with suspected stroke had brain imaging. Brain computed tomography (CT) was done using Toshiba Aquilian, 128 slices computed tomography, initially on admission and MRI brain with stroke protocol if indicated. 1.5 Tesla GE Signa Explorer MRI machine was used for patients undergoing MRI in order to access the site and size of the infarction. The site of infarctions were determined according to the vascular territory along largest diameter of the lesion. Images were reported by a radiologist at radiology department, Rehman Medical Institute, Peshawar.

All the patients meeting inclusion criteria were given high intensity statin as a part of secondary stroke prevention. High Intensity Statin are defined as dose of statin expected to lower LDL C by 50% or greater. It include atorvastatin 40-80mg/day and Rosuvastatin 20-40mg/day.[4]

Patients were divided randomly into 2 groups based on statin type. Group1 was given Atorvastatin 40mg/day and group 2 was given rosuvastatin 20mg /day. Baseline modified Rankin Scale along with CPK, TSH, ALT , renal profile and Low density lipopreotein (LDL) were recorded. Short term effect of high intensity statins were measeured at 6 weeks of discharge. On follow up LDL was measured, symptoms and signs of myopathy along with serum CPK level were recorded. The patients having myopathy were categorized as per Statin related myopathy (SRM) classification. Standardized nomenclature and classification of SRM is following.[15]

SRM 0 : asymptomatic elevations in serum creatine kinase (CK) <4 the upper limit of normal (ULN)

SRM 1 : Myalgias (aches, cramps and/or weakness)

with no CK elevations.

SRM 2: Myalgias (aches, cramps and/or weakness) with minor CK elevations (<4 ULN)

SRM 3: Represents increasingly infrequent myopathy with CK >4 but <10 ULN

SRM 4: is severe myopathy with CK >10 but <50 ULN;

SRM 5: Constitutes rare but potentially life-threatening rhabdomyolysis with either CK >10 ULN, muscle symptoms and renal impairment, or CK >50 ULN

SRM 6: Consists of very rare anti-HMGCR positive immune-mediated necrotizing myopathy, which persists despite statin cessation.

2.2 Data Analysis:

For all cases, we recorded Age, gender, mRS, type of stroke, previous stroke or TIA, history of myopathy, drug history, thyroid, liver or renal dysfunction. On admission CPK, TSH, ALT, LDL was recorded. To see the short term effect of high intensity statins, symptoms/signs of myopathy, CPK and LDL were recorded at 6 weeks. All the data was recorded in pre designed proforma.

Data was entered and analyzed by SPSS 24. For quantitative variables like age mean±SD was calculated and for qualitative variables like gender, stroke type, and SRM. Frequencies and %ages were calculated. On the basis of myopathy , study population was divided into two groups. Both groups were compared in terms of age, gender, mRs, Premorbid status and type of statin used. Chi square test was applied. Keeping in view the unequality of two groups, P value derived from fisher exact test was considered. Further more, adjusted analysis in form of logistic regression was carried out to support association.

3. RESULTS

A total of 202 patients were included in the study out of whom 13 patients were lost to follow up and were therefore excluded from analysis. Out of the remaining 189 patients 59.8% (113) were males whereas (40.2%) 76 were females. The Mean age of patients included was 62.25 ±11.83 years. The Mean LDL (low density lipoprotein) at admission was 121.43±21.56 mg/L.

67.7% (126) of the patient had associated comorbidities. Diabetes Mellitus was present in 43.4% (83) 52.9%(100) were hypertensive and 12.2%(23) had Ischemic Heart Disease.

According to Bamford classification of ischemic stroke, 39.2%(74) of the strokes were partial anterior circulation strokes (PACS) whereas lacunar stroke (LACS) and posterior circulation syndrome (POCS) comprises 22.8%(43) each. 11.1% (21) suffered from TACS. 57.5%(108) of the patients had a Modified Rankin Scale (mRS) score of less than 3. 51.9%(98) of the participants received 40 milligrams of atorvastatin rest received rosuvastatin.

The Mean Low density lipoprotein LDL level at 6 weeks follow-up were 61.12 ± 27.29. mg/dl. The mean reduction in LDL level was 50% over the period of 6 weeks. 70.9% (134) of the patients achieved an LDL level of <70 mg/dl. 22.2%(42) patients had LDL level in the range of 70-100 mg/dl. while only 6.9% (13) of the patients had LDL>100 mg/dl on follow up.

Regarding myopathy, no patient developed myalgias or muscle tenderness/weakness on examination upon follow up. However, 4.2% (8) patients had raised CPK on follow-up. This patients group fell into SRM 0 category as per the definition described above. None of the patients suffered from any other type of SRM.

Table 1. Comparison of Myopathy and non myopathy groups

Factors		Group1 (SRM)	Group 2 (Non SRM)	P value
Age(mean)		58.12±13.52	62.43±11.76	0.2
Gender	Male	50%(4)	60.2%(109)	0.71
	Female	50%(4)	39.8%(72)	
mRs on discharge	<3	62.5%(5)	56.9%(103)	1.0
	≥3	37.5%(3)	43.1%(78)	
Statin drug	Atorva	25%(2)	53%(96)	0.15
	Rasuva	75%(6)	47%(85)	
Premorbid states	DM	50%(4)	43.1%(78)	0.72
	HTN	25%(2)	54.1%(98)	0.15
	IHD	0%(0)	12.7%(23)	0.59
LDL at 6 weeks	<70	75%(6)	70.7%(128)	0.73
	70-100	25%(2)	22.1%(40)	
	>100	0%(0)	7.2%(13)	

We further classified the study population into two groups. Group 1 was comprised of patients who developed SRM, and the second group comprised of patients who did not develop SRM. We compared the two groups to see any positive association with the development of SRM. Factors like age, gender, mRs, type of statin, premorbid and LDL levels at 6 weeks were compared between SRM and non SRM groups. No statistical significance was observed.

No significant association of myopathy was found. This was further confirmed by applying logistic regression. Detail can be seen in table 2.

Table 2: Logistic Regression analysis

Factors	OR (95% CI)	P value
Statin		
Myopathy	3.38 (.666-17.236)	.141
Model1+ age	3.125 (0.605-16.14)	.174
Model2+gender	3.091 (.598-15.987)	.178
Premorbids		
Myopathy	2.068(.500-8.558)	.316
Model1+ age	2.090 (.503-8.692)	.311
Model2+gender	2.099 (.504-8.739)	.308
HTN		
Myopathy	3.542 (.696-18.021)	.128
Model1+ age	3.612(.707-18.459)	.123
Model2+gender	3.738 (0.727-19.221)	.115
mRs		
Myopathy	.792(.184-3.416)	.755
Model1+ age	0.848(.195-3.69)	.826
Model2+gender	0.816(.185-3.589)	.778

4. DISCUSSION

High intensity statins are recommended by international stroke guidelines.[4] Approximately 73.9% of Randomized controlled trails data regarding statin therapy has been based upon white populations. Data from Asia contributes only 4% to the total evidence in this regard.[8]

However, sparse data from Asia still supports the use of high intensity statins. High-intensity statin in secondary prevention of stroke reduced the risk of re stroke by 16% at 5 year followup.[19] More over, In a large study conducted in Tiawan, patients receiving high intensity statins had a lower rate of ischemic stroke as compared to patients receiving non high intensity (adjusted HR: 0.803, 95% CI:0.670-0.961) at 3 year follow up. The difference was more pronounced in female gender.[20]

In Asian perspective, debate is going on regarding statin use. Current Taiwan Lipid Guideline emphasizes the importance of "treat-to-target", but not "statin intensity" strategy. They have increased the LDL target to <100 mg/dl as compared to <70mg/dl set by international guidelines.[20] While they themselves have documented increase risk of stroke in non high intensity group on followup in the same study.

On the other hand, 'Treat stroke to target trail' states that LDL target 70 is superior to 90-110 mg/dl for preventing major atherosclerotic events.[4] More over, Lyengar et al from India has recommended that high intensity statin therapy is needed to reduce the LDL level to clinically meaningful limit, as set by AHA. However, a concern about the tolerability of high intensity statins in terms of myopathy wasn't taken into account.[21]

Another school of thought, in favour of high intensity statin, is to manage South Asian population more aggressively than western population keeping in view the high risk of atherosclerotic diseases in them.[9]

Based on international data, high-intensity statins are preferred by 73.7% physicians in a survey conducted in India.[9] However, the lack of evidence at regional level combined with fear of increase risk of myopathy has led to reluctance in prescribing high intensity statin by physician or/and low adherence to high intensity statin by patient.[6,7,22]

The magnitude of statin induced myopathy has been debated widely. The prevalence vary in different studies because of the difference in assessment tool and ethinicty. Observational studies described that 10% - 15% of patients suffer from myopathy while on statin standard dose [23,24] while clinical trails have given its prevalence upto 30%.[25,26] Only few studies from Asia has been carried out to elaborate this fact. In a study including patients suffering from myocardial infarction in Taiwan, stated no difference of hospitalization for myopathy between high and non high intensity statin groups at 3 years followup, however there was dose reduction observed in 8.2% patients in high intensity group as compared to 1.4% in non high intensity group. The reason wasn't elaborated for this dose reduction.[13]

A study from Pakistan was carried out on patients suffering from acute coronary syndrome reported mylagias in 80.08% patients receiving high intensity Atorvastatin and 85.27% receiving high intensity

Rosuvastatin.[27]However in this study the objective evidence of myopathy was not taken by measuring muscle enzymes, more over there was a significant confounder bias due to concomitant prescription of cardiac medication causing drug inhibition resulting in elevated plasma concentration of statins.

Another cross-sectional study from Pakistan described that statin related myalgias can be reduced from 10% to 4% if alternate day statin regimen is used.[28]The major limit of this study was that the rationale and efficacy of alternate day statin regimen was not taken into account. More over lipid lowering effect was over looked for this alternate day regimen. Thirdly no objective assessment of statin induced myopathy was considered, results just relied on patient's history.

On the other hand, A large REAL CAD trail supported the use of high intensity statin in patients of Coronary artery disease as no adverse effect were seen in Japanese population, more over high intensity statins reduced the all cause mortality significantly.[17]

Like wise, a Cohort study was carried out to compare the risk of high intensity related myopathy in Chinese ethnicity versus non Chinese. Chinese were not associated with risk of myopathy hazard ratio being 0.61 (95%CI 0.28 to 1.34), when compared to non Chinese.population.[29]

Our study takes the lead of being 1st study from Southeast Asia describing high intensity statin related myopathy in stroke Population. All studies done before those are discussed above are carried out on coronary artery patients. In our study outcome was measured by proper SRM classification. We described that 4.2% of study participants suffered from asymptomatic myopathy falling in category of SRM0. The diagnosis was supported by serum CPK level, none of our patients developed any other form of SRM at 6 weeks follow up. These results are similar to Chinese and Japenese studies but contradictory to few studies done in Asia as narrated above. However Asian studies carried some limitation described above to weaken their results.

Regarding risk factors of developing statin induced myopathy, literature describes its positive association with multiple factors like female gender, old age, concomitant drugs usage, underlying thyroid disease, history of creatinine kinase elevation, intensity and type of statins, excessive physical activity and Asian ethnicity.[23,30] Keeping in view the possible associations, we excluded patients with thyroid diseases, baseline raised creatinine kinase and those who are taking drugs with potential association with statins. In stroke patients we took mRs score as a replacement of physical activity. We didn't find any positive association with age, gender, type of statin, presence of premorbid and mRs. This difference can be explained on the basis of ethnic difference.

Our study highlights two points. First, high intensity statins didn't cause myopathy even after 6 weeks of initiation of therapy. Secondly, with high intensity statin 70.9% study population achieved LDL of <70mg/dl, that is the target set by guidelines. However the dose of statin used in our study was the minimum recommended dose to classify them as high intensity drug. In Western countries, far more dosage are being used even with addition of other lipid lowering drugs to achieve LDL targets.[31,32] The reason for this difference can be explained by the Racial differences in the response to statins between Asian and West population. The difference is usually explained by pharmacokinetics of drug and partially by genetic factors.[11]

Short comings of our study are that it is a single center study so the results can't be generalized to the whole population. Secondly, our results are based upon short term assessment of the patients ie 6 weeks. Further multicenter studies focusing on long term effect of high intensity statins are required to strengthen the results of this study.

With this study , we have provided the evidence that use of high intensity statin are safe in our population, this is the time to act according to the current global guidelines with regard to statin use in secondary prevention of stroke in order to cut off the risk of restroke attributed to dyslipidemia.

5. CONCLUSION

A very small number of the study population developed evidence of minor, asymptomatic myopathy (SRM0). None got symptomatic myopathy. There was no significant association of myopathy with age, gender, mRs, premorbids and type of statin used. Moreover, with high doses we managed to achieve desired LDL in a significant number of people on 6 weeks follow up. The statin doses required to achieved LDL target in our study population was quiet less than doses required to lower LDL in Western population.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	WQ, MSI
Acquisition, Analysis or Interpretation of Data:	WQ, MSI, SK, ZAY, MFK, RAK
Manuscript Writing & Approval:	WQ, MSI, SK, ZAY, MFK, RAK

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.