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Role of Atorvastatin in Prevention of Intracranial artery Stenosis

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Abstract
Objective: To find out the role of atorvastatin in prevention of intracranial artery stenosis**Study Design:** Observational study**Place and Duration of Study:** We conducted this study in department of Medicine Nishter Hospital Multan and Ganga Ram Hospital Lahore from June 2017 to June 2018. **Methodology:** Forty two patients were selected for this study and every patient received clopidogrel and aspirin to prevent further cerebral infarction or transient ischemic attack. Group A and group B were formed. There are twenty one patients in Group A and they received atorvastatin 10mg per day. Twenty one patients of group B received atorvastatin 40 mg per day. VCT scanner was used to check out the effects of atorvastatin on the perfusion. . Descriptive data was compared by applying Independent T test and Chi-square test was applied on nominal data. Data was analyzed using SPSS v.23 and value of $p \leq 0.05$ was considered statistically significant. **Results:** At 1 month visit, he incidence of TIA and cerebral infarction was 9.5% and 9.5% in group A and 4.7% and 4.7% in group B, respectively (p=0.678). At 12 month visit, he incidence of TIA and cerebral infarction was 23.8% and 19% in Group-A and 4.7% and 4.7% in group-B, respectively (p=0.049). The difference was statistically significant.**Conclusion:** In our study we came to the conclusion that the use of atorvastatin is associated with decrease in risk of TIAs and stroke in patients of intracranial artery stenosis.
Keywords: Atorvastatin, Intracranial artery stenosis, statins, prevention.

Introduction

One of the major reasons of the ischemic stroke all over the world is the stenosis of the intracranial arteries.[1] Intracranial arteries include basilar artery, vertebral arteries, internal carotid artery and middle cerebral artery. The main process involved in the stenosis of the intracranial arteries is atherosclerosis. Atherosclerosis occur as a result of injury to the blood vessel and as a result of the injury cholesterol starts to deposit in the injury site and over a period of time it form plaques in the wall of the artery. [2 3] As a result of this plaque formation the diameter of the arteries become narrow and the blood flow to that part of the brain is decreased which results in transient ischemic attack or stroke which in turn can cause even death of the person. Asian, African and Hispanic are mostly affected by intracranial artery stenosis.[4] As far as the symptoms of intracranial artery stenosis are concerned they range from sudden weakness, numbness of arms, legs, loss of vision. Above mentioned symptoms usually affect one side of the body and the other side is not affected. Other symptoms of intracranial artery stenosis are confusion, loss of balance, blurring of vison, dizziness and headache. Causes of intracranial artery stenosis is same as the causes of atherosclerosis i.e. smoking, diabetes, hypertension, obesity, heart disease, family history advance age, high level of cholesterol, arterial dissection, moyamoya disease and fibromuscular dysplasia.[5] Magnetic resonance angiography (MRA), CT angiography, angiogram, transcranial Doppler ultrasound, CT perfusion and positron emission tomography are the interventions usually used to diagnosed intracranial artery stenosis.[6]

To control the risk of stroke and to decrease the progression of intracranial artery stenosis both medical and surgical interventions are used. In surgical treatment our main objective is to open up the artery which is causing the reduction in blood supply to the brain. We achieve this aim by doing balloon angioplasty/stenting and cerebral artery bypass. [7] Surgical interventions are used only when all the medical interventions become useless. In medical treatment of intracranial artery stenosis the main objective is to treat the cause of ICAS. Anticoagulants (aspirin, Coumadin and clopidogrel) lipid lowering drugs and blood pressure controlling drugs (beta blockers, ACE inhibitors, diuretics and calcium channel blockers) are used in the management of intracranial artery stenosis.[8] Statins belong to the lipid lowering category of the drugs and they are wildly used in the treatment of intracranial artery stenosis. Atorvastatin is the drug mainly used for this purpose. Atorvastatin decreases the cholesterol production in the body by inhibiting the 3-hydroxy-3-methylglutaryl –coenzyme A reductase (HMG co-A). [9] This enzyme involves in conversion of HMG-co-A to mevalonate and thus stops the synthesis of cholesterol in the body. [10] Atorvastatin is not given to the patients with liver disease, pregnant patients and highly elevated levels of CPK, AST and ALT. As far as the side effects of atorvastatin are concerned they include myopathy, peripheral neuropathy, myositis, muscle cramps, anorexia, jaundice, hepatitis and pruritus etc.

In this study we are going to see the dose related effect of atorvastatin in prevention of intracranial artery stenosis. We are going to compare our results with the other studies and will find out the quantity of atorvastatin dose most appropriate to control intracranial artery stenosis.

Material n methodology

In this study observational method of study is used. We conducted this study in department of Medicine Nishtar Hospital Multan and Ganga Ram Hospital Lahore from June 2017 to June 2018. Approval for the conduction of study was obtained from the hospital committee. Every patient was informed about the procedure of this study and only those persons were included in the study who gave their consent. Sample size was calculated from the reference study performed by Peiyang Z et al. Patients with the diagnosis of atherosclerosis of large artery in accordance with TOAST criteria, stenosis of middle or basilar cerebral artery greater than or equal to fifty percent established on CT angiography were included in this study. Patients with clinical diagnosis of transient ischemic attack and the diagnosed cases of acute ischemic attack and transient ischemic attack were also included in the study. Patients in whom the level of low density lipoprotein (LDL) is greater than 3.6 mmol/L with normal liver function were also eligible for inclusion into the study. Patients with greater than fifty percent of extracranial stenosis on same side, patients of intracranial hemorrhage, cerebral embolism and cerebral infarction were excluded from the study. Patients with heart, liver lung disease, patients with non-atherosclerotic stroke and who have allergy to statins were also excluded from the study.

Forty two patients were selected for this study according to the above mentioned criteria by two consultants. Each patient included in our study received clopidogrel and aspirin to prevent further cerebral infarction or transient ischemic attack. Two consultant neurologists examine the patients on follow-ups during the duration of study. They recorded about the cerebral infarction points during the follow-up visits. Group A and Group B were formed. There are twenty one patients in Group A and they received atorvastatin 10mg per day. Twenty one patients of group B received atorvastatin 40 mg per day. Sixty four layer light speed VCT scanner was used to check out the effects of atorvastatin on the perfusion. Before scanning 40 ml of iohexol and 20 ml of normal saline was infused into the patient's body. Five seconds after injecting iohexol scanning was done and the scanned images were analyzed by workstation software and pseudo color function charts of perfusion parameters like cerebral blood volume (CBV), cerebral blood flow (CBF) and time to peak (TTP) were obtained. These images were used to find out the relative value of the cerebral blood volume (rCBV), relative cerebral blood flow (rCBF) and relative time to peak (rTTP). Relative values were obtained by using the images of the region of the interest and its center is used to create mirror image on the opposite side and on opposite side values of cerebral blood flow, cerebral blood volume and total time to peak were notes on 4 points and this is how we obtained our relative values. These values were used to assess the effect of treatment on the patients and the average value of these points was noted to find out the response. Descriptive data was compared by applying Independent T test and Chi-square test was applied on nominal data. Computer software SPSS version 23 was used to statistically analyze the data. P value of less than or equal to 0.05 was taken as significant.

Results

Calculated N=42 (two groups; 21 in group-A atorvastatin @ 10mg/day; 21 in group-B atorvastatin @ 40mg/day) (Chi-square test and independent-t test)

At 1 month visit, he incidence of TIA and cerebral infarction was 9.5% and 9.5% in Group-A and 4.7% and 4.7% in group-B, respectively (p=0.678). At 12 month visit, he incidence of TIA and cerebral infarction was 23.8% and 19% in Group-A and 4.7% and 4.7% in group-B, respectively (p=0.049). The difference was statistically significant. Table-I

CTP parameters including rCBF, rCBV and rTTP were calculated at 1 month visit and the difference was not statistically significant (p-value 0.692, 0.265 and 0.064, respectively). When the rCBF, rCBV and rTTP values were measured at 12 month visit, there was statistically significant difference between the two groups with p-values 0.023, 0.036 and 0.008, respectively. Table-II

Table-I

Incidence of events at 1 month and at 12 months visit, N (%)

Visit	Events	Group-A (n=21)	Group-B (n=21)	Total (n=42)	p-value
At 1 month	TIA	2 (9.5)	1 (4.7)	3 (7.1)	0.678
	Cerebral Infarction	2 (9.5)	1 (4.7)	3 (7.1)	
At 12 month	TIA	5 (23.8)	1 (4.7)	6 (14.3)	0.049
	Cerebral Infarction	4 (19)	1 (4.7)	5 (11.9)	

TIA = transient ischemic attack

Table-II
CTP parameters prior to and after treatment

Time	Parameter	Group-A (n=21)	Group-B (n=21)	p-value
Prior to Treatment	rCBF	.72±.04	.73±.07	0.692
	rCBV	.77±.09	.80±.09	0.265
	rTTP	1.31±.10	1.25±.11	0.064
After Treatment	rCBF	.77±.09	.84±.106	0.023
	rCBV	.82±.08	.88±.09	0.036
	rTTP	1.32±.09	1.24±.08	0.008

Data is entered as mean ± S.D. rCBF = relative cerebral blood flow; rCBV = relative cerebral blood volume; rTTP = relative time to peak

Discussion:
In our study we came to the conclusion that the use of atorvastatin is associated with decrease in the risk of TIA and stroke in patients of intracranial artery stenosis. We also found out that by increasing the dose of atorvastatin chance to develop stroke and TIA decreases more drastically. Peiyang Z et al. [11] they conducted a study on patients with intracranial artery stenosis and they divide them into 3 groups in order of increasing dose of atorvastatin and found out that high dose of atorvastatin is more useful in preventing the risk of cerebral infarction as compared to the low dose of atorvastatin. Jong-Won C et al. [12] in their study they came to the conclusion that the use of statin in patients with intracranial stroke is associated with stabilization of the plaques and thus causing decrease in the risk of stroke and transient ischemic attack.

Christine A et al. [13] found out that the aggressive use of statin is more beneficial to the patients to intracranial artery stenosis as compared to stenting the artery. Ping g [14] et al. conducted this study on the Chinese patients in order to find out the effect of intensive statin therapy in preventing intracranial artery stenosis and they concluded that the long term use of statins is associated with reduction in the rate of cerebrovascular events with same adverse effects as low dose therapy. Hye-jin K et al. [15] in their study found out that the use of statins in high doses in the patients of intracranial artery stenosis is associated with reduction in the advancement of disease process. Nakano E et al. [16] did their study on the patients with low LDL level and they found out that statins are beneficial in these patients in preventing cardiovascular disease. Sookyung R et al. [17] in their study concluded that the early therapy with rosuvastatin results in the lessening in the symptoms of the cerebrovascular disease. kyu S et al. [18] came to the conclusion that progression of basilar artery stenosis can be preventing by using high doses of statins.

Conclusion: In our study we came to the conclusion that the use of atorvastatin is associated with decrease in the risk of TIA and stroke in patients of intracranial artery stenosis. We also found out that by increasing the dose of atorvastatin chance to develop stroke and TIA decreases more drastically.

Conflict of interest: Nil

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