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Some Effects of Statins on Ischemic Stroke: A Review.

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ABSTRACT

Stroke is widely effect on health quality around the world. High incidence of stroke, make this disease as a problem for health providers. Recently, some advantages of statins about prophylaxis from stroke incidence and neuroprotective effects are discussed. Beyond the lipid lowering effect of statins, these drugs have other benefits for patients that have risk factors of stroke or chance of recurrent stroke. This review will discuss the some advantages of statins application in stroke patients. We summarized the common statins mediated mechanisms in ischemic stroke patients such as anti-oxidative effect, effect on Matrix metalloproteases, Pathway of eNOS-mediated, nitric oxide, blood pressure and atherosclerosis, and also lipid lowering levels.

Keywords: statins, ischemia, stroke

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INTRODUCTION

Stroke is the third leading cause of mortality in the United States. There are more than 700 000 incident strokes every year and about 4.4 million stroke survivors(1). A major portion of stroke incidence is initial episodes whereas about 200000 cases are recurrent stroke incidence. Up to 30% of survivors developed to permanent disability and within 3 months after stroke incidence, up to 20% of patients will require institutionalization. Direct and indirect costs of stroke and its complications in 1999 was estimated by the American Heart Association to be $51 billion(2). The prevalence of stroke in 2010 was about 33 million with 16.9 million new unset strokes. Now, globally stroke is the second leading cause of death after cardio vascular disease(3).

Stroke is categorized to two groups of ischemic and hemorrhagic. Ischemic stroke takes place after an artery that supplies oxygenates blood to the brain tissue becomes blocked. The most common cause of blockage that leads to ischemia is blood clot. Ischemic stroke is divided to two subgroups; embolic and thrombotic. The consequence of blood leakage or rupture of brain arteries lead to hemorrhagic stroke. The blood leakage increase intracranial pressure and cause damage. Hemorrhagic stroke have two subtypes; intracerebral and subarachnoid(4). All types of stroke would be provoked by some risk factors. "Some important risk factors are; age**:** The effect of aging on the cardiovascular system over a period of time significantly increases stroke risk. For example, systolic blood pressure increases with age.

Some Hispanic Americans and Blacks have high stroke incidence and mortality rates in comparison with whites (the incidence of stroke in blacks is 38% more than whites). High prevalence of obesity, diabetes mellitus and hypertension can effect on the incidence of stroke in black population.

Family History is another factor that influence on stroke incidence. Parental history of stroke may be effect of chance of stroke incidence. Possible reasons include genetic heritability, other familial factors such as environmental and cultural factors, and the interaction between genetic and environmental factors.
Also hypertension is an important risk factor for stroke. Systolic and diastolic hypertension, increase the chance of stroke incidence. In an statement that presented by Goldstein et al, the relationship between stroke and hypertension is direct, and independent"(1).

Some other risk factors of stroke are abdominal obesity, diet, previous stroke, sex, transient ischemic attack, or systemic embolism diabetes mellitus, alcohol intake, physical activity and psychosocial factors. Serum concentration of lipids such as triglycerides, low-density lipoprotein [LDL], high-density lipoprotein [HDL], cholesterol and triglyceride are recently regarded as a risk factor for cerebrovascular disease(1, 5).

Based on a meta-analysis results, no association was found between cholesterol and stroke rate. But in some other studies, a clear association between total serum cholesterol and stroke incidence were found(6). Some studies presented that there is a weak relation between serum cholesterol and higher risk of cerebral infarction in ischemic stroke. Overlay, there are controversy if hyperlipidemia can effect on stroke incidence or not. Recently statins are widely prescribed to lower the serum cholesterol concentration in patients with ischemic heart disease and stroke. More than lipid lowering effect of statins, these drugs have other advantages in stroke(7). Also among Ischemic Stroke patients, treatment with statins is associated with lower mortality in administration period and better functional outcomes. The aim of this study is evaluation of statins role in prevention and treatment of stroke.

In high risk population, a decrease in cholesterol level via statins use reduces the incidence of stroke. This effect of statins is seen in patients with stroke or transient ischemic attack. performing preventing strategies (antithrombotic treatment and lowering blood pressure) in combination with a 1 mmol/L decrease in LDL cholesterol level can considerably decrease incidence of stroke(8, 9).

Effect on lipids:

"Based on a meta-analysis of data from cohort studies, there is no association between the risk of stroke and total cholesterol concentration, while in another meta-analysis with larger population study, an obvious association between total cholesterol concentration and ischemic stroke before age 70 years"(8).

Strokes categorized as hemorrhagic or ischemic. Ischemic stroke includes small-vessel disease, cardioembolic, atherothrombotic, and other subtypes. Hemorrhagic stroke has subtypes includes intracerebral, subarachnoid, and subdural(10). The relation between cholesterol concentration and each of these underlying pathological conditions is seems to be different(11). "Evidences show that a dose–response relation is found between serum cholesterol concentration and probability of ischemic stroke and an inverse relation between hemorrhagic stroke and cholesterol concentration. In a cohort study, after 19 years follow up, the association between stroke and LDL cholesterol concentration was not significant(12). However, regarding to the age and gender, incidence of lacunar stroke and atherothrombotic stroke substantially rose with increasing levels of LDL cholesterol"(8). As it mentioned above, LDL cholesterol concentration has no significant relation with incidence of stroke, but the results of another systematic review showed that serum concentration of HDL cholesterol, is inversely associated with stroke risk and carotid atherosclerosis(13). In a meta-analysis that evaluated the stroke prevention strategies, only low concentration of HDL was related to the recurrent strokes(14). In patients who had ischemic type of stroke, HDL cholesterol concentration has an effective role rather than other types of stroke(15). Regarding to recant findings, triglyceride concentrations were associated with recurrent stroke. Also triglyceride concentration can strongly predict incidence of all types of strokes(16).

However, the serum concentration of LDL cholesterol is not a predictor of stroke, even in patients with carotid stenosis. Same findings were reported in another subanalysis that aimed to evaluate protection strategies against recurrent stroke. They found no association between risk of recurrent stroke incidence and baseline LDL cholesterol concentration(17).

"In a meta-analysis, showed that total cholesterol to HDL cholesterol ratio is strongly predictive of future stroke risk in in contrast with HDL, non-HDL, or total cholesterol concentrations"(8).

Effect on stroke

Many studies have not clarified a relation between the possibility of occurrence of ischemic stroke and some clinical conditions such as dyslipidemia. However, some studies those focused on coronary artery disease prevention, showed that there is an association between statins with a reduction in stroke risk(6).

One of the most effective drugs in lowering serum cholesterol concentrations and preventing ischemic heart disease (IHD) and cerebrovascular disease, are statins. This drug family is widely prescribed for the prevention of vascular events. "Actually they are inhibitors of 3-hydroxy-3-methyl-glutaryl-CoA reductase those reduce the risk of stroke incidence with aggressive reduction in cholesterol level"(18). This enzyme effects on cholesterol biosynthesis via limiting the rate of the mevalonate pathway for in non-hepatic tissues and the liver and catalyzing the early conversion of HMG-CoA to mevalonic acid(6). statins reduce total cholesterol content in the liver, via negative-feedback on LDL receptor upregulation and other subsequent those have role in lowering total serum cholesterol levels. Each member of this family, in reducing LDL have some different in absorption, solubility,excretion, binding, and variable dose-related efficacy(19).

"Statins' action results in a variety of pleiotropic effects. This property includes stabilization of atherosclerotic plaque, reduction in inflammation level, endothelial function improvement, and altered thrombogenicity"(6). "On the other hand many other studies present results that suggest the reduction in stroke risk in patients with statins use while no coronary artery disease was detected in them. some trial studies provide strong support for statin therapy to reduce stroke risk in patients with average or low LDL cholesterol levels. These data support the role of statins to prevent stroke independent of reduction in coronary artery disease risk or levels of serum lipids"(20).

Effect on Stroke outcome

Evidence demonstrates that long-term statin treatment reduces risk of stroke. "A number of studies support that statins might have benefit for better stroke outcome. There are controversies about the effect of long term statin use as a pre-treatment drug in patients with no history of previous CVA but have some risk factors such as coronary artery disease, acute neuroprotective effect in patient who started use of these drugs after CVA incidence and ability of this type of drugs in secondary stroke prophylaxis or promoting regeneration of nervous system. Animal model experimental studies show that in stroke and tissue damage after focal brain

ischemia statins can improve the clinical outcome"(6). Long-term statin use as pretreatment protocol increases the level of "eNOS" expression in the platelets and in vasculature, augments absolute cerebral blood flow, also decreases markers of platelet activation, diminishes lesion volume and after occlusion of middle cerebral artery and reperfusion in the mouse improves neurologic function(21). Also eNOS upregulation by statin treatment can ameliorate cerebral vasospasm that caused by subarachnoid hemorrhage. Statins increase the level of eNOS expression agment NO bio-availability via mechanisms those are dependent or independent to cholesterol. Endres and colleagues demonstrate that after 14days of statin pretreatment, increases in cerebral blood flow were also observed in the hemisphere that have ischemic lesion. This effect of statins (Increasing Blood Flow) could be used as a useful way for increasing the delivery of co-administered drugs and other therapeutic modality to the ischemic tissue. Increasing blood flow in ischemic brain tissue reduces cerebral infarct size. Chopp and colleagues demonstrated that prolonged oral administration of statins such as atorvastatin and simvastatin 1 day after focal cerebral ischemia in rats, induce brain plasticity and enhance functional outcome(6, 22).

"The ability of statins to effects on neurogenesis, angiogenesis, and synaptogenesis would be result in neuro-restoration effects. For example, 1to3 mg/kg atorvastatin increase cell proliferation in the dentate gyrus and subventricular zone, increase in vessel density and vascular endothelial growth factor (VEGF) in the ischemic brain tissue, inhibition of astrocytic activation, enhanced synaptophysin immunoreactivity (Chen et al, 2003). Also in neonatal ischemia, morphologic and behavioral consequences of ischemic and hypoxic brain injury would have better prognosis by administration of statins. Also statins directly activate eNOS via protein kinase Akt, which is a regulator of cellular processes such as apoptosis and metabolism. Activation of Akt, acutely increase the production of NO and gradually increase the endothelium dependent vasodilation. This effect of statins obviously precedes cholesterol production.

The antithrombotic role of statins is another important effect of this family during brain infarction. In addition high dose statins reduce thrombus formation and some markers of platelet activation. Regulation of fibrinolytic balance as a provoking factor in up regulating tissue plasminogen activator and inhibiting plasminogen activator inhibitor is another effect of statins. Other advantages of statins use are anti-oxidative and Anti-inflammatory and immune-modulatory activities. Inhibition of NADPH and Rac1 by statins reduces the activity of superoxide radicals within vascular cells. There are evidences that statins diminish a number of inflammatory markers such as soluble intercellular adhesion protein or interleukin-6 and C-reactive protein. Anti-inflammatory effect reduces the risk of atherosclerosis and also neuro-degeneration via interaction of LFA-1 with intercellular adhesion molecule"(6).

Direct effects of statins on the immune system on B-cells and macrophages (via inhibiting the interferon-induced expression of MHC class II), suggesting a role for statins in immune-modulation(23).

Neuro-protective effects

In addition to lipid lowering property of statins, evidences show that this family has also neuro-protective effects via modulating inflammatory mediators. In a review article, Wang and colleagues presented some aspect of neuroprotective of statins. Their results is mentioned below(7).

"Effect on Matrix metalloproteases (MMPs): MMPs are enzymes that destruct the extracellular proteins (e.g. collagen), release thrombotic stuff into the peripheral bloodstream and consequently effects on extracellular matrix remodeling and also has a role in neuro-inflammatory response. Studies showed that MMP levels in the brain tissue is significantly up regulated by recombinant human tissue plasminogen activator (rht-PA), leads to the corruption of blood brain barrier. Statins abolished the upregulation of MMPs levels leading to reduction of MMP mediated blood brain barrier permeability.

Anti-oxidative effect: as it said before, anti-oxidant effect of statins is a way to protect neurons. During ischemic stroke significant amounts of anti-oxidants or reactive oxygen species are produced in damaged cells. ROS directly cause cell damage by generating cyclooxygenase, xanthine dehydrogenase, xanthine oxidase and NADPH oxidase.

Pathway of eNOS-mediated: it has been suggested that the activation of eNOS mediated pathway has advantages for patients with ischemic stroke. Production of eNOS cause vasodilatory effect that result in an

increase in cerebral blood flow. In vitro studies showed the protective effects of statin on cerebral blood flow were abolished in eNOS knockout mice.

Effect on nitric oxide: nitric oxide has a key role in signaling in the vascular system and modulates the cerebral blood flow by increasing a potent vasodilative response that is associated with the progression of vascular dementia. Statins increase NO production via upregulating eNOS. Also statins stop over production of NO by downregulating the iNOS and nNOS.

Effect on blood pressure and atherosclerosis: one of the most important causes of vascular dementia is atherosclerosis. A study showed that atherosclerosis leads to eNOS dysfunction, reduction in eNOS expression in rabbits while statins have anti-sclerotic effect with ameliorating the eNOS function. Anther risk factor of vascular dementia is hypertension. Statins decrease systolic and diastolic pressure. However, low systemic blood pressure results in hypo perfusion that subsequently causes the risk of ischemic injury. The property of blood pressure lowering seems to be a double edge sword"(7).

CONCLUSION

Based on studies those reviewed in this study, statins have an important role in stroke prevention and outcome. many mechanisms such as lipid lowering levels, and cholesterol independent mechanisms (such as effect on nitric oxide levels, pathway of eNOS, anti-oxidant elements and Matrix metalloproteases) effect on incidence and outcome of patients. Decreasing serum lipid levels with statins is effective to reduce the incidence of initial and recurrent stroke. Randomized statin trials show a 18% reduction in stroke incidence rather than control individuals. Statins decrease the incidence of ischemic stroke via Stabilization of atherosclerosis, antithrombotic and hematological properties witch reduce plaque disruption and thromboembolism of artery to artery. Also makes some changes on cerebral vessels by increasing blood flow and possibility of reperfusion chance in brain parenchyma are potentially neuroprotective. These cholesterol independent neuroprotective properties of statins can be used clinically to promote prognosis of patients with ischemic stroke.

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