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The Relationship of Low Density Lipoprotein (LDL) Cholesterol Level with Haemorrhagic Transformation of Acute Cerebral Infarct

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Abstract

Background: Acute ischemic stroke (AIS) is characterized by the sudden loss of blood circulation to an area of the brain, typically in a vascular territory, resulting in a corresponding loss of neurologic function. Although stroke often is considered a disease of elderly persons, one third of strokes occur in persons younger than 65 years. Risk of stroke increases with age, especially in patients older than 64 years, in whom 75% of all strokes occur. The system of categorizing stroke developed in the multicenter Trial of ORG 10172 in Acute Stroke Treatment (TOAST) divides ischemic strokes into the following 3 major subtypes:

- Large-artery
- Small-vessel, or lacunar
- Cardioembolic infarction

Large-artery infarctions often involve thrombotic insitu occlusions on atherosclerotic lesions in the carotid, vertebrobasilar, and cerebral arteries, typically proximal to major branches; however, large-artery infarctions may also be cardioembolic. Cardiogenic emboli are a common source of recurrent stroke. They may account for up to 20% of acute strokes and have been reported to have the highest 1-month mortality. Small vessel or lacunar strokes are associated with small focal areas of ischemia due to obstruction of single small vessels.

Ischemic and hemorrhagic stroke cannot be reliably differentiated on the basis of clinical examination findings alone. Further evaluation, especially with brain imaging tests (ie, computed tomography [CT] scanning or magnetic resonance imaging [MRI]), is required. The prevalence of hemorrhagic transformation (HT) after acute ischemic infarction varies greatly. Risk factors of HT include ageing, severity of stroke, baseline hypertension, hyperglycemia and cardioembolic infarction and low levels of low-density lipoprotein (LDL). We investigated the relationship between LDL, lipid profile and HT after acute ischemic infarction and suggested precautions for HT management.

Methods: Fifty-four patients with acute infarction were included in the study. Fasting lipid profile was examined on the next morning following hospitalization. Either MRI brain or CT was performed, in follow up to detect any cerebral microbleed (CMB) and hemorrhagic transformation. The lipid profiles examined included total cholesterol (TCH), triglyceride (TG), LDL and high-density lipoprotein (HDL).

Results : Among all the patients, HT was noted in 20 patients and non-HT in 34. As compared with non-HT group, HT group had lower levels of LDL, but higher

scores of NIHSS, higher rates of diabetes mellitus, higher BP and the older age group(>65years). The study showed that cardioembolic infarction, infarction with undetermined etiology, high scores of NIHSS, diabetes, hypertension and dyslipidemia were the risk factors of HT.

Conclusion : Low level of LDL is likely associated with increased HT after acute ischemic infarct. So for those patients who are having low level of LDL, higher blood sugar, high HbA1c, and hypertension at the time of admission, aggressive lipid- lowering treatment should be prescribed cautiously to prevent the incidence of haemorrhagic transformation.

Key Words: Acute ischemic infarction; Hemorrhagic transformation; Hyperglycemia, hypertension; Low-density lipoprotein cholesterol**.**

Introduction

Acute ischemic stroke (AIS) is characterized by the sudden loss of blood circulation to an area of the brain, typically in a vascular territory, resulting in a corresponding loss of neurologic function. An acute vascular occlusion produces heterogeneous regions of ischemia in the affected vascular territory. Affected regions with cerebral blood flow of lower than 10 mL/100 g of tissue/min are referred to collectively as the core. These cells are presumed to die within minutes of stroke onset. Zones of decreased or marginal perfusion (cerebral blood flow < 25 mL/100g of tissue/min) are collectively called the ischemic penumbra. Tissue in the penumbra can remain viable for several hours because of marginal tissue perfusion. Risk factors for ischemic stroke include *modifiable* and *non-modifiable* conditions. Identification of risk factors in each patient can uncover clues to the cause of the stroke and the most appropriate treatment and secondary prevention plan.

Non-modifiable risk factors include the following (although there are likely many others):

- Age
- Race
- Sex
- Ethnicity
- History of migraine headaches [20]
- Fibromuscular dysplasia
- Heredity: Family history of stroke or transient ischemic attacks (TIAs)

Modifiable risk factors include the following :

- Hypertension (the most important)
- Diabetes mellitus
- Cardiac disease: Atrial fibrillation, valvular disease, heart failure, mitral stenosis, structural anomalies allowing right-to-left shunting (eg, patent foramen ovale), and atrial and ventricular enlargement
- Hypercholesterolemia
- Transient ischemic attacks (TIA)
- Carotid stenosis
- Hyperhomocystinemia
- Lifestyle issues: Excessive alcohol intake, tobacco use, illicit drug use, physical inactivity
- Obesity
- Oral contraceptive use/postmenopausal hormone use
- Sickle cell disease

Strokes can be divided into 2 types: hemorrhagic or ischemic. According to the World Health Organization (WHO), 15 million people suffer stroke worldwide each year. Of these, 5 million die, and another 5 million are left permanently disabled. Men are at higher risk for stroke than women; while men have a stroke incidence of 62.8 per 100,000, with death being the final outcome in 26.3% of cases, while women have a stroke incidence of 59 per 100,000 and a death rate of 39.2%.

Hemorrhagic transformation (HT), which refers to a spectrum of ischemia-related brain hemorrhage, is a

frequent spontaneous complication of ischemic stroke, especially after thrombolytic therapy (1). Therefore, HT limits the use of tissue plasminogen activator (tPA) treatment, the only method of clinical management of acute ischemic stroke. To search for new treatments as well as intervention measures for HT, it is important to understand its underlying mechanism and identify its predictors. The occurrence of hemorrhagic transformation (HT) after acute ischemic brain infarction varies from 8.5% to 30% of the patients being affected. HT includes hemorrhagic infarction (HI) and parenchymal hematoma (PH), and symptomatic HT is the most severe type, which usually occurs after thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) and is the predictive factor for poor prognosis **(1)**. Active exploration of the risk factors of HT has important clinical significance in reducing the occurrence of symptomatic HT and improving the life quality of patients. Recent studies suggest that the risk factors of HT include advanced age, severity of stroke, baseline hypertension, high scores of NIH Stroke Scale (NIHSS), hyperglycemia and cardioembolic infarction, dyslipidemia **(2,3)**. Kim et al **(4)** indicated that low levels of low-density lipoprotein (LDL) might be related to HT among the patients of atherosclerotic cerebral infarction. However, it is unclear whether lipid profile is related to HT for patients with all types of ischemic stroke. The current study investigated the relationship between baseline lipid levels and HT in consecutively included patients with acute ischemic infarction, and the results suggested that low level of LDL is likely associated with increased HT after acute ischemic infarction. With regard to the type of hemorrhage, HT can be divided into hemorrhagic infarction (HI) and parenchymal hematoma (PH) . HI is a heterogeneous hyperdensity occupying a portion of an ischemic infarct zone on computed tomography (CT) images, whereas PH refers to a more homogeneous, dense hematoma with mass effect. Each of them has two subtypes: HI type 1 (HI1) and HI type 2 (HI2) for HI and PH type 1 (PH1) and PH type 2 (PH2) for PH. On radiographic images, HI1 is characterized by small hyperdense petechiae, whereas HI2 refers to more confluent hyperdensity throughout the infarct zone. Both of the two types are without mass effect. PH1 refers to the homogeneous hyperdensity occupying less than 30% of the infarct zone, with some mass effect, and PH2 refers to the homogeneous hyperdensity occupying over 30% of the infarct zone, with significant mass effect. The rate of HI is higher than that of PH. Petechial hemorrhage is thought to be a marker of good outcome, possibly because it indicates early reperfusion to still viable brain tissue. Nonetheless, in either petechial or parenchymal hemorrhage the cause of bleeding is injury to and/or remodeling of blood vessels which form the blood–brain barrier (BBB) and are part of the neurovascular unit.

Material And Methods

There were 54 patients of cerebral infracts admitted and given written consent in the medicine department at LLRH, GSVM MEDICAL COLLEGE Kanpur, during period of December 2016 to October 2017 are included in this study.

Methods of collection of data

Study design: Observational prospective study.

Sample size: minimum of 50 patients.

Exclusion criteria:

1)Age less than 18 years

2) Cases of parenchymal and subarachnoid hemorrhages.

3) pregnant woman

Inclusion criteria:

1) age more than 18 years

2)patient willing for follow up radiological investigation

3)written formal consent

4)patients having radiological evidence of ischemic infract at presentation

Methodology: A complete medical history of all the patients who were included in the study was taken, in which particular stress on past history of hypertension, diabetes mellitus, old CVA. All the patients were subjected to investigate like complete hemogram, CT/ MRI of brain, blood sugar level, serum lipid profile, HbA1c level, LFT and KFT. The patients were given the tablet aspirin 150 mg and HMG CO A reductase inhibitors, the statins (atorvastatin 20mg).

Statistical Analysis: A student 't' test was done and the results were considered to be statistically significant when 'p' value is <0.05 and highly significant when 'p' <0.001.

Results

In our study, risk factors for HT were studied in 54 patients of cerebral infarct during period of December 2016 to October 2017 in the LLR Hospital in department of medicine.The following results were found :

Graph 1-Correlation of Hemorrhagic Conversion with LD.

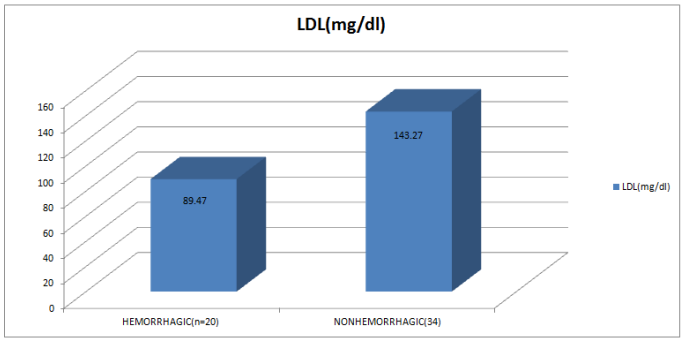

Table 1-Correlation Of Hemorrhagic Conversion With Ldl Cholesterol

Risk Factor	Hemorrhagic(N=20)	Nonhemorrhagic(N=34)	p-value
	Mean ±SD	Mean ±SD	
LDL Cholesterol(mg/dl)	89.47±12.36	143.27±19.88	0.001

Out of 54 patients 20 patients had hemorrhagic conversion whose LDL level was low; the mean value was 89.47 mg/dl and 'p' value was <0.001 which was statistically highly significant.

Graph 2 : Correlation Of Haemorrhagic Conversion With Total Cholesterol Level.

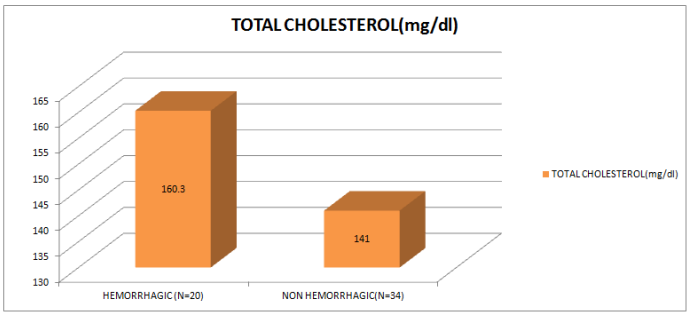

Table 2 : Correlation Of Haemorrhagic Transformation With Total Cholesterol Level.

RISK FACTORS	*HEMORRHAGIC (n=20)*	*NON-HEMORRHAGIC(n=34)*	
	Mean ±SD	*Mean ±SD*	*P value*
TOTAL CHOLESTEROL(mg/dl)	*160.35±42.35*	*141.08±29.18*	*.05*

Out of 54 patients 20 patients had hemorrhagic conversion whose Total cholesterol level was high; the mean value was 160.35 mg/dl and 'p' value was 0.05 which was statistically significant.

Graph 3- Correlation of Hemorrhagic Conversion With HDL Cholesterol Level.

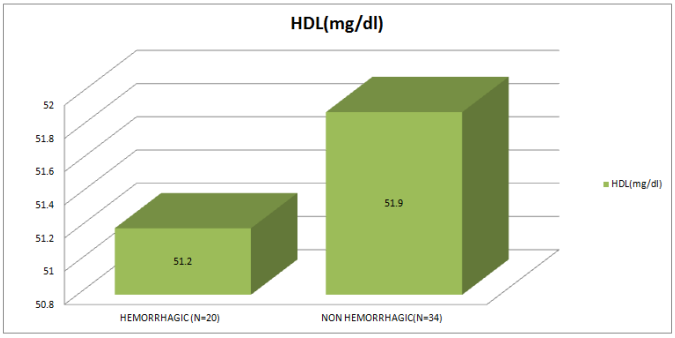

Table 3- Correlation Of Haemorrhagic Conversion With HDL Cholesterol Level.

RISK FACTOR	HEMORRHAGIC(n=20)	Non-hemorrhagic(n=34)	
	Mean ±SD	Mean ±SD	P value
HDL CHOLESTEROL(mg/dl)	51.20±13.21	51.97±9.59	.08

Out of 54 patients 20 patients had hemorrhagic conversion whose HDL level was 51.20 and in non-hemorrhagic patients, mean HDL was 51.97 with p value 0.08 which was statistically not significant.

Graph 4- Correlation of Hemorrhagic Conversionith Triglyceride Level.

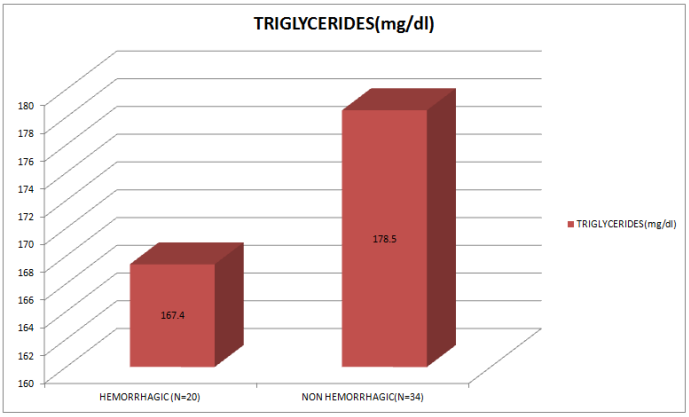

Table 4 – Correlation Of Haemorrhagic Conversion With Triglycerides Level.

RISK FACTOR	HEMORRHAGIC(n=20)	NONHEMORRHAGIC (n=34)	
	Mean ±SD	Mean ±SD	P value
TRIGLYCERIDES (mg/dl)	167.4±63.29	178.58±45.86	0.45

Discussion

The exact pathogenesis of HT after acute ischemic stroke is not yet established. HT may result from the damage of blood brain barrier due to acute ischemic infarction or secondary cerebral edema, injury after ischemia reperfusion, or adverse effects of thrombolysis with recombinant tissue type plasminogen activator (rt-PA) or urokinase, etc. Although Carlos et al **(5)** suggested that thrombolysis-related hemorrhagic infarction may represent early successful recanalization and lead to a reduced infarct size and improved clinical outcome, symptomatic parenchymal hematomas was an independent predictor of increased early mortality and poor functional outcomes at 3 months **(6)**. Animal experiments and epidemiologic studies have demonstrated that increased incidence of spontaneous cerebral hemorrhage is associated with low levels of Total Cholesterol **(7,8,9),** and recent evidence suggests that LDL cholesterol concentration is inversely related to incident intracerebral hemorrhage **(10)**. However, up to now there is no prospective study to explore the correlation between lipid profile and HT after acute ischemic stroke, so the relationship is still not definitive.

The current study included consecutive inclusion of patients with acute infarction, which consists of several types of ischemic stroke according to TOAST **(11)** (e.g. arteriosclerotic infarction, small vessel infarction, cardioembolic infarction, undetermined etiology infarction). Risk factors were recorded and MRI GRE-T2/CT Head was performed to diagnose HT in all patients. We found that compared with non-HT group, HT group had higher levels of Total Cholesterol with significant difference ($p<0.05$) and lower levels of LDL with highly significant differences ($p<0.001$). The multivariate logistic regression showed that low level of LDL increased the incidence of HT and there was no significant relationship between HT and HDL. In conclusion, low level of LDL was inversely related to HT. In addition, cardioembolic infarction, undetermined etiology infarction, high scores of NIHSS and diabetes were the risk factors of HT. Kim et al **(4)** also reported that a low level of LDL cholesterol was independently associated with HT in large artery atherothrombotic, but not in cardioembolic infarction. However, D'Amico et al **(12)** retrospectively analyzed the correlation of HT and lipid levels at admission in a consecutive series of 240 patients with anterior ischemic

stroke, and suggested that a lower TC and lower LDL-C levels are associated with an increased risk of HT. Uyttenboogaart et al **(13)** assessed a prospective hospital-based stroke registry and discovered that high admission triglyceride levels were independently associated with a higher risk of symptomatic HT, but total cholesterol levels, LDL levels and statins use had no influence on both the occurrence of symptomatic HT or functional outcome. Rocco et al **(14)** found that in an open, prospective study of 1,066 stroke patients undergoing thrombolysis therapy, neither the lipid profile nor prior statins use were associated with increased odds of symptomatic HT, functional outcome or mortality at 3 months. The pathogenic mechanisms by which the low level of LDL increased the risk of HT are not yet established. The increased symptomatic hemorrhagic transformation after recanalization therapy for ischemic stroke was correlated with lower admission low-density lipoprotein cholesterol level. But after acute ischemic stroke or transient ischemic attack, an aggressive lipid-lowering treatment with 80 mg of atorvastatin per day was associated with a 66% increase in the relative risk of hemorrhagic stroke as compared with placebo. An adequate level of the lipid may maintain the integrity of the small cerebral vessels, while the too lower level of lipid will destroy the integrity of the small vessels and result in blood extravasation over the unstable integrity of endothelial cells in the small cerebral vessels. After severe ischemic infarction, especially complicated with sepsis and other critical illness, the integrity of the small cerebral vessels was vulnerable to damage.

Conclusion

On the basis of our study,we conclude that, for those patients with high-risk Haemorrhagic transformation, aggressive lipid lowering treatment should be prescribed with caution. In addition, for those patients without prior lipid lowering treatment, lower lipid levels may reflect poor general medical condition and increases the risk for Haemorrhagic transformation. Moreover, the development of myopathy or hepatic dysfunction from statins may also be increased in the critically ill patients. So, the administration of aggressive lipid-lowering treatment for severe stroke patients should be individualized considering each patient's likelihood to benefit or be harmed, and should be based on future high-quality clinical evidence.

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