

Original Research Article

Blood lipid levels, statin therapy and risk of intracerebral hemorrhage versus ischemic vascular events: a prospective case control study from tertiary care center of south India

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ABSTRACT

Background: Intracerebral hemorrhage (ICH) is characterized by high mortality and morbidity. A little is known about the association between blood lipids, statin use and risk of ICH. Objective of the study was to investigate the relation between blood lipid levels and risk of hemorrhagic stroke.

Methods: Prospectively compared the lipid levels of primary ICH patients (case) with ischemic group (control) patients, i.e. age and sex matched individuals admitted from January 2014 to January 2015 and outcome analyzed.

Results: Of the 678 acute stroke patients, 78 (11.5%) had ICH who was enrolled. Mean age was 53±14.4. ICH was frequent in older age (57.6%) with male gender predominance (73%). Most frequent location of bleed was in thalamus (30.7%). Low density lipoprotein (LDL), triglyceride (TG) and very low density lipoprotein (VLDL) cholesterol were significantly low in ICH patients compared to controls. There was no significant difference in the high density lipoprotein (HDL) levels in both groups. Mean total cholesterol was significantly low in a subset of study group that included male gender, younger onset stroke (<50 years) and with prior history of hypertension. Subgroup analysis in ICH group showed significantly low mean total cholesterol, LDL and TG cholesterol in statin group compared to non-statin group.

Conclusions: Lower blood lipid levels are associated with an increased risk of ICH. The reduction of blood lipids due to statin therapy might increase the risk of ICH, especially in hypertensive individuals and those with alcohol use; hence there should be a cautious use of statins.

Keywords: Lipids, ICH, Risk, Statins

INTRODUCTION

ICH is the second most common subtype of stroke after ischemic stroke and accounts for approximately 10% to 20% of all strokes and is characterized by high mortality and morbidity.¹ Dyslipidemia is an important risk factor for ischemic stroke and statins use significantly decrease risk of recurrence of ischemic stroke. However the association between lipid levels, statins use and risk of ICH is controversial and not clear.

Most research studies have shown that lower total cholesterol, lower LDL cholesterol, and higher HDL were associated with increased risk of ICH.² However the association between TG and VLDL and risk of ICH is not clear.

In the present study we prospectively recruited patients with symptomatic ICH in a case control design to know the relationship between individual lipid fractions and risk of ICH.

METHODS

A prospective study with case control design was conducted between January 2014 and January 2015 at Employees State Insurance Corporations (ESIC) Superspeciality hospital Hyderabad. During this period out of 678 cases of acute stroke admitted, 78 patients with symptomatic ICH were enrolled in the study. ICH was defined as bleeding within the brain parenchyma manifesting as acute onset of focal neurological deficit. ICH was confirmed by non-contrast computed tomography (CT). Secondary causes of hemorrhage such as hemorrhagic infarct, venous thrombosis, antecedent trauma, central nervous system tumor, vascular malformations and bleeding diathesis were excluded.

Serum lipid profile was obtained in fasting state within 24 hours of admission. Information regarding the relevant variables in the study was collected comprising age, sex, risk factors, co morbid illness, clinical presentation, serum lipids level, and outcome of stroke with the help of structured proforma. Outcome was assessed at 3 months period using modified Rankin scale.

The control group comprised of 78 patients who had ischemic stroke, and were admitted during the same period, age and sex matched to the case group (ICH).

Data obtained in the study were subjected to statistical analysis with statistical package for social science version

18. Bivariate analysis was done to know the proportion of individuals with low lipid fractions among ICH cases and control group using chi square test. A two tailed probability value <0.05 was considered significant. Multivariate analysis was done using logistic regression.

RESULTS

Baseline characteristics

Of the 678 acute stroke patients admitted, 78 (11.5%) patients had primary intracerebral hemorrhage (ICH) who was enrolled in the study. Age range of study sample was 18 -82 years. Mean age was 53±14.4. Of the 78 cases 57 were males and 21 were females. ICH was frequent in older age (>50 years) observed in 45 patients (57.6%). ICH patients were compared with age and sex matched ischemic patients (control group) who were admitted during the same period. Baseline characteristics of study group are shown in Table 1.

44 patients (56.4%) in ICH group were hypertensive, 34 patients (43.5%) were alcoholic, 23 patients (29.4%) were smoker and 9 patients (11.5%) were diabetic. The proportion of patients with diabetes mellitus ($\chi^2=10.64$, P=0.001), alcohol use ($\chi^2=7.47$, P=0.006) and smoking ($\chi^2=4.6$, P=0.03) was significantly low in ICH group compared to ischemic group. 16 patients (20.5%) were taking statins.

Table 1: Baseline characteristics of study group (ICH versus ischemic group).

Risk factors	ICH group (n=78)	Control (n=78)	Chi square	P value
Diabetes	9 (11.5%)	26 (33.3%)	10.64	0.0011
Hypertension	44 (56.4%)	52 (66.6%)	1.73	0.18
Coronary artery disease	6 (7.6%)	11 (14.1%)	1.65	0.19
Statin use	16 (20.5%)	17 (21.5%)	0.14	0.70
Alcohol use	34 (43.5%)	51 (65.3%)	7.47	0.006
Smoking	23 (29.4%)	36 (46.1%)	4.60	0.03

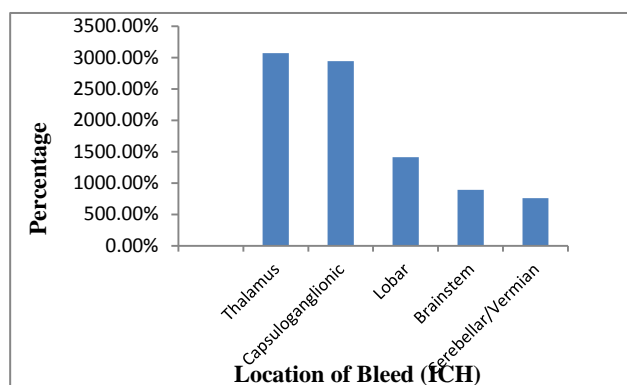


Figure 1: Location of bleed.

ICH location

67 patients (85.8%) had deep parenchyma bleed and 11 patients (14.1%) had lobar bleed. The most frequent location of bleed was in thalamic region observed in 24 patients (30.7%) followed by capsuloganglionic bleed in 23 patients (29.4%), lobar bleed in 11 patients (14.1%), brainstem bleed in 7 patients (8.9%) and Cerebellar hemisphere and vermin bleed in 6 patients (7.6%) (Figure 1). Obstructive hydrocephalus was observed in 3 cases that had Cerebellar hemisphere bleed. Death occurred in 2 cases.

Serum lipids

The range of total cholesterol in ICH group was 75-268 mg/dl compared to control (68-406mg/dl). Low total cholesterol (TC<160 mg/dl) was higher in ICH patients compared to controls (48% vs. 37%). There was a significant decrease in LDL (P-value=0.0028), TG (P-value=0.022) and VLDL cholesterol (P-value=0.022) levels in patients with ICH compared to ischemic stroke patients. Decrease in total cholesterol and increase in HDL cholesterol in ICH patients was not found to be significant compared to ischemic group (Figure 2).

Subgroup analysis of study group based on gender, it was observed that the mean total cholesterol was significantly low in men in the ICH group compared with ischemic group (P-value=0.005) whereas in a subgroup analysis based on age (patient with age <50 years was compared in both groups) it was observed that the mean total cholesterol was significantly low in ICH patients (P-

value=0.004) compared to control group. There were no significant differences in mean total cholesterol levels in women and patients greater than 50 years of age between study groups. Table 2 shows the mean and standard deviation of lipids in study group.

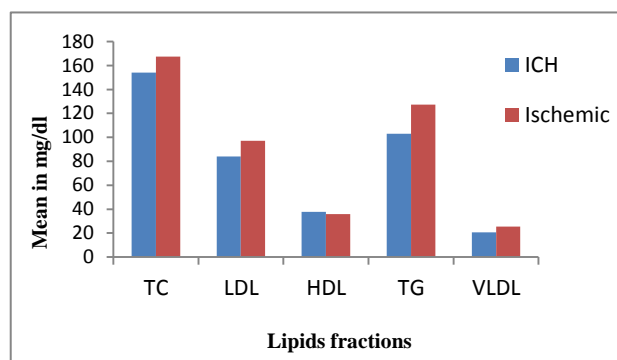


Figure 2: Comparison of lipid fraction among study group.

Table 2: Comparison of mean and standard deviation of lipids in study group.

Serum lipids (mg/dl)	ICH group (n=78)		Ischemic group (control)		T value	P value
	Mean	Std deviation	Mean	Std deviation		
Total cholesterol	154.00	48.21	167.44	48.47	1.76	0.08
LDL cholesterol	84.07	33.75	96.99	38.81	2.21	0.028
HDL cholesterol	37.84	10.70	35.97	9.03	1.17	0.24
Triglycerides	103.10	54.77	127.34	74.13	2.3	0.022
VLDL cholesterol	22.62	10.95	25.47	14.83	2.3	0.022
Total cholesterol in men (n=57)	144.2	39.7	161.07	34.8	2.41	0.017
Total cholesterol in women (n=21)	183.7	55.8	184.7	72.1	0.05	0.96
Total cholesterol >50 years	151.7 (n=45)	53.4	160.2 (n=49)	42.8	0.85	0.39
Total cholesterol <50 years	157.03 (n=33)	40.57	179.5 (n=29)	55.4	1.83	0.071

Table 3: Comparison of mean and standard deviation (Std deviation) among hypertensive patients in ICH group and Ischemic group.

Lipids (mg/dl)	ICH hypertensive group (n=44)		Ischemic hypertensive group (n=52)		T value	P value
	Mean	Std deviation	Mean	Std Deviation		
Total cholesterol	154.20	49.20	175.83	51.10	2.10	0.038
LDL -C	89.55	38.23	103.13	42.11	1.64	0.10
HDL -C	38.05	11.19	35.92	9.43	1.01	0.31
Triglyceride	103.89	59.11	139.41	79.14	2.45	0.016
VLDL-C	20.78	11.82	27.88	15.83	2.45	0.016

(LDL-C low density lipoprotein cholesterol, HDL-C high density lipoprotein cholesterol, and VLDL-C Very low-density lipoprotein cholesterol).

In a subgroup analysis of patients with hypertension, the mean total cholesterol (P-value=0.03), Triglyceride level (P-value=0.01) and VLDL values (P-value=0.007) were

significantly low in ICH group compared to control (Table 3). Further subgroup analysis in patients with diabetes, it was observed that there was no significant

mean difference in lipid parameters between both groups. In subgroup analysis of patients with history of alcohol use it was observed that mean LDL cholesterol in patients with ICH was significantly low (P-value=0.014) compared to ischemic group.

Statins use

In a subgroup analysis patients with statins use in ICH group (n=16) were compared with statins use in Ischemic group (n=17), it was observed that mean total cholesterol

was significant low in ICH group (P-value=0.03) (Table 4).

ICH patients were subdivided into statins group (n=16) and non-statins group (n=62), comparison of mean, standard deviation, t value and p value is shown in Table 5. Mean total cholesterol (P-value= 0.003), LDL cholesterol (P-value=0.02) and TG (P-value=0.03) were significantly low in the statins ICH group compared with non-statins ICH group.

Table 4: Comparison of lipids between intracranial hemorrhage (ICH) statins use group and Ischemic stroke statins use group.

Lipids	ICH statins use group(n=16)		Ischemic statins use group(n=17)		T value	P value
	Mean	Std deviation	Mean	Std Deviation		
TC	122.75	20.45	162.7	70.71	2.17	0.03
LDL	67.13	21.21	80.17	30.34	1.42	0.16
HDL	35.9	11.89	35.11	10.87	0.19	0.84
TG	77.31	30.09	100.82	50.15	1.16	0.11
VLDL	15.25	5.85	20.06	10.01	1.67	0.10

Table 5: Comparison of mean and standard deviation of cholesterol with statins and non-statins subgroup of intracranial haemorrhage (ICH).

Lipids	Statins group (ICH)(n= 16)		Non- statins group (ICH) (n=62)		T value	P value
	Mean	Std deviation	Mean	Std deviation		
TC	122.75	20.45	162.06	50.09	3.06	0.003
LDL	67.13	21.21	88.44	35.10	2.31	0.02
HDL	35.9	11.89	38.33	10.41	0.80	0.42
TG	77.31	30.09	109.27	57.86	2.12	0.03
VLDL	15.25	5.85	23.21	15.78	1.97	0.05

There was no significant correlation observed between individual variables such as diabetes, hypertension, alcohol use, age and lipid parameters in patients with ICH (P-value >0.05).

DISCUSSION

Hyperlipidemia is a proven risk factor of ischemic stroke.³ Many epidemiological and case control studies showed low lipid levels as risk factor for ICH, especially for hemorrhage due to hypertensive vasculopathy.⁴⁻⁶ This was attributed to the fact that lipids especially cholesterol and TG are essential component of cell membrane and play an important role in maintaining the stability of cerebral blood vessels.⁷

So far our study has been first of its kind that compared blood lipids and use of statins in ICH and ischemic group and being the largest from India. Our data confirms that individual with lower cholesterol levels are at increased risk of ICH. We observed a significant decrease in LDL,

TG and VLDL cholesterol in patients with ICH compared to Ischemic group. However there was no significant difference in mean total cholesterol and HDL cholesterol observed in both groups.

Studies by Suzuki et al showed low mean total cholesterol was associated with risk of ICH, this was not observed in present study.⁸ Instead subgroup of patients who belong to male gender, patients with younger onset stroke (<50 years), hypertensive's, those with statins use had significant low mean total cholesterol in ICH patients compared to Ischemic patients. This may be due to fact that here we compared with ischemic group than with normal control group. Our findings are against the prospective study reported by Zhang et al, where significant low total cholesterol was associated with risk of ICH in women, but not in men.⁵

Bonaventure et al in his study demonstrated that low levels of TG was associated with a more than two fold increased risk of ICH.⁴ Similar findings were observed in present study (P value= 0.022). Level of HDL cholesterol

positively correlated with risk of ICH, suggesting that increased level of HDL cholesterol may be related to higher risk of ICH.⁵ However in the present study no significant difference in HDL level and occurrence of ICH was observed.

A different impact of cholesterol, according to etiology of ICH has been observed in our study. Patients with history of hypertension had a significant lower mean total cholesterol, TG and VLDL levels in ICH group when compared to ischemic group. Our findings are consistent with previous studies which confirm the role of low lipids and risk of ICH specifically for hemorrhage due to hypertensive vasculopathy.^{4,6} Mean LDL cholesterol was significantly lower in ICH patients with alcohol when compared with ischemic group. This is attributed to the fact that LDL cholesterol level decreased significantly as alcohol intake increased.⁹ Our data suggests that low LDL level in combination with alcohol use is significantly associated with risk of ICH (P value= 0.014). The role of LDL in vessel fragility needs to be further explored.

Statins have been widely used clinically. There is a concern whether lowering lipid levels by statin therapy may increase the risk of ICH. SPARCL study demonstrated that low cholesterol level was associated with less risk of recurrent ischemic stroke, but the post hoc analysis found that there were more hemorrhagic stroke patients in treatment group (Ischemic stroke) than those in placebo group.^{10,11} Present study also it was observed that mean total cholesterol was significantly low in ICH group who were on statins use either due to previous ischemic stroke or coronary artery disease. Subgroup analysis in ICH group showed significantly low mean total cholesterol, LDL and TG in statins group compared to non-statin group. Present study further confirms that statin therapy increased the risk of ICH among patients who had been treated with simvastatin or atorvastatin.

CONCLUSION

The study found that lower LDL, TG and VLDL cholesterol levels had a higher risk of ICH. Mean low total cholesterol was considered to be risk factor of ICH in a subset of study group only (Men, younger stroke and hypertensive's). The reduction of blood lipids caused by statin therapy might increase the risk of ICH, especially in hypertensive individuals, and those with alcohol use. Therefore patients with low lipids and high risk of ICH, there should be a cautious use of statins. Further research with larger subset of populations may establish a deeper insight in present study especially with reference to the dosage of statins which could predispose to ICH in patients with risk factors.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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