Bangladesh Crit Care J March 2018; 6 (1): 26-30

Original Article

Is low total cholesterol associated with primary intracerebral hemorrhage in Bangladeshi population?

Md. Anwarul Kibria[1], Md. Hassanuzzaman[2], Pradip Kumar Kayasthagir[3], Md. Rabiul Karim[4], Asifur Rahman[5], Abu Saleh Mohammad Abu Obaida[6], Zaman Ahmed[7], Mahfujur Rahman Babul[7], Akramul Azam[7], Md. Golam Faruk[7]

Abstract

Background: *This study was carried out to see the association of the low total cholesterol level with primary Intracerebral Hemorrhage (ICH) in Bangladeshi population.*

Materials and Methods: *This was a case–control study carried out in the department of Neurology, Chittagong Medical College and Hospital from January 2013 to December 2013. Total of 132 patients were enrolled where 67 patients of hemorrhagic stroke were in the experimental group and 65 age and sex matched persons were in the control group. Low total cholesterol was designated as level less than 200mg/dl. Data were analyzed and compared by SPSS version 19.*

Results:*The proportion of ICH patients with low total cholesterol was significantly higher than the controls (74.6% vs. 32.3%). Mean total cholesterol was also significantly low in ICH patients compared with controls (180 mg/dL vs. 217 mg/dl; P-value = 0.001). Low-density lipoprotein cholesterol (LDL-c) and triglycerides were also significantly low in ICH patients compared with controls. Mean LDL-c in the ICH patient group was 106 mg/dL, whereas it was 128.5 mg/dL in the control group (P-value = 0.001). There was no significant difference in the high-density lipoprotein (HDL) levels in both groups. Although lower mean cholesterol was seen in both young and older individuals in the ICH group than in controls, the difference was significant only in the older group (age >60 years). In multivariate analysis, odds ratio of low cholesterol in the hemorrhage cases was 6.03 (95% CI = 2.1–16.059) which was adjusted other risk factors of hemorrhagic stroke.*

Conclusions: *The inference of this study is that, there is an increased risk of primary ICH associated with low total cholesterol, especially in older individuals.*

Key Words: *Intracerebral Hemorrhage (ICH), Total Cholesterol, Low-density lipoprotein cholesterol (LDL-c)*

Introduction:

Intracerebral Hemorrhage (ICH) is a common occurring condition in the older population. Cholesterol levels play important role in pathology of ICH. Different studies have demonstrated positive association of higher serum cholesterol levels with ischemic stroke and cardiovascular disease. But the association between the serum cholesterol level and the risk of intracerebral hemorrhage is inverse.[1]

Cholesterol is essential for all animal life, which is synthesized in each cell from simpler molecules in a complex 37-step process. Cholesterol is essential for many normal bodily functions. Enzymes use cholesterol to produce vitamin D, steroid hormones (estrogen, progesterone and testosterone), stress hormones and bile acid for digestion. Cholesterol forms a membrane that surrounds all cells and is also a critical part of regenerating damaged endothelial cells. Cholesterol is actually a "healing agent" and is needed to produce new cells whenever healing is required. For example, cholesterol levels drastically increase after surgery, infections and even heart attack as part of healing process[2]. Cholesterol is recycled and excreted through liver in a non-esterified form (via bile) into the digestive tract. Typically about 50% of the excreted cholesterol is reabsorbed by the small bowel back into the bloodstream.[3]

Low serum total cholesterol is designated as fasting total cholesterol < 200 mg/dl[4]. In Asian population, where plasma cholesterol levels are low, hemorrhagic stroke may form up to 30% of all strokes.[5] Although other factors probably also contribute to this high frequency of intracerebral hemorrhage (ICH), low cholesterol levels have been proposed as one explanation for the high incidence of ICH in these countries.

1. Lecturer, Department of Anatomy, Chittagong Medical College.
2. Associate Professor, Department of Neurology, Chittagong Medical College
3. Assistant Professor, Department of Neurology, Chittagong Medical College.
4. Assistant professor, Department of Neurosurgery, Chittagong Medical College.
5. Assistant Professor, Department of Neurosurgery, Bangabandhu Sheikh Mujib Medical University.
6. Medical Offficer, Department of Neurosurgery, Bangabandhu Sheikh Mujib Medical University.
7. MD (Neurology) Thesis part student, Chittagong Medical College.

Corresponding Author:

Dr. Md. Anwarul Kibria
MBBS, MD (Neurology)
Lecturer, Department of Anatomy, Chittagong Medical College
Email : drkibria2017@gmail.com,
Mobile : +8801811529915

The explanation for a higher incidence of intracerebral hemorrhage in those with low cholesterol levels is unclear. Cholesterol and triglyceride play important role in cell membrane. There is increased erythrocyte fragility and decreased platelet aggregation ability *in vitro* and *in vivo* with reduced levels of cholesterol. It has been proposed that lower cholesterol results in a weakened endothelium that hemorrhages[6,7]. Potentially weakened endothelium may be more susceptible to micro aneurisms, the chief pathological finding of cerebral hemorrhage[8].

It remains unclear whether low cholesterol directly promotes ICH by these or other mechanisms. It is perhaps equally likely that the relationship might be based on a common underlying factor rather than a direct causal link. Alternatively, the finding may reflect an effect of dietary differences, such as protein deficiency or substitution of saturated with polyunsaturated fatty acids[9]. Studies also showed the only cause of death attributable to serum cholesterol concentration was hemorrhagic stroke.[10]

We carried out this study to see if there is any association of low total cholesterol level with increased incidence of ICH.

Materials & Methods:

This case control study which was performedin the Department of Neurology, Chittagong Medical College & Hospital, Chittagong, from January 2013 to December 2013 for a duration of 01 (one) year, after obtaining necessary ethical permission from the IRB(Institutional Review Board) of Chittagong Medical College.

A total number of 132 subjects were enrolled in this study, where 65 patients of hemorrhagic stroke were taken as cases and 65 age and sex matched subjects were taken as control. Sampling technique was purposive sampling. Inclusion criteria were radiologically (C.T scan of Head) documented hemorrhagic stroke within 5-7 days of stroke occurrence. Patients were aged between 18 to 80 years. Patients with history of head trauma, CNS tumor, patients on anticoagulants, antiplatelet, drug abuse and patients with arterio venous malformation were excluded from the study.

Detailed history regarding age, sex, socioeconomic status, known medical diseases and risk factors of stroke were taken from each subject. Through general examination, nervous system and other systemic examination were done. Physical examination and examination for focal neurological sign were carried out with special attention.

5 (Five) ml of blood was collected from each selected subjects for analysis of lipid profile at fasting state and analysis was done under Department of Biochemistry with Dimension series autoanalyzer, Siemens, USA by automated method.

The data were analyzed with the help of Statistical Package for Social Science (SPSS - 19). Descriptive statistics were presented in frequencies, percentages and 95% confidence intervals. Quantitative variable was analyzed by mean, standard deviation and t-test. Qualitative variable was analyzed & presented with frequency and chi-square test. Regression analysis was done where necessary. P value of <0.05 was considered statistically significant.

Results

A total number of 67 cases of hemorrhagic stroke and age and sex matched 65 subjects were taken as control, were enrolled in the study. **(**Table I**)** 53.7% were male and 46.3% were female in case group and it was 56.9% and 43.1% respectively in control group.

Maximum patients were below 60 years in both study & control groups. **(**Table II**)**.Regarding age of case and control it was matched (P>0.05)

Table –II shows distribution of the *age* among the study groups

Among the risk factors that is diabetes mellitus, Hypertension, cigarette smoking, obesity and low cholesterol were analyzed. **(**Table-III**)** It was found that hypertension (P<0.05) and low cholesterol (P<0.05) were highly significant. Cigarette Smoking was also found to be significant.

Table –III shows risk factors among the study groups

In analysis of biochemical variables, serum total cholesterol, LDL and triglyceride (TG) were found significantly low in case group then in control group (P<0.001). **(**Table-IV**)** HDL was found to be non-significant in any group.

Table –IV shows analysis of biochemical variables like serum total cholesterol, LDL, TG

With regression analysis it was found that hypertension, age >60 years and low serum cholesterol were of very high significant value. **(**Table-V**)** DM, cigarette smoking and obesity were found to be insignificant in development of ICH.

Table –V: shows regression analysis of risk factors

Discussion

The prevalence of hemorrhagic stroke in populations with low serum cholesterol has been reported in different population-based studies. One likely explanation for this observation is an inverse relationship between hemorrhagic stroke and serum cholesterol[2]. In Asian population, where plasma cholesterol levels are low, hemorrhagic stroke may form up to 30% of all strokes[5]. Low total cholesterol plays an important role along with other risk factors in developing high frequency of intra cerebral hemorrhage (ICH). So, this present case control study is designed to find the relationship between primary ICH and low cholesterol in our context.

Among the 67 patients suffering from hemorrhagic stroke, lowest age was 25 years and highest age was 90 years. Majority of the patients were above 50 years (61.1%). We found that the mean age of the stroke patients were 56.30±13.88. Previously, one study[11] showed mean age to be 59.61±13.20 years which matches with our findings. Age more than 60 years were found increasingly associated with hemorrhagic stroke (OR 2.45; 95% CI=0.79-7.30; p=0.018).

Table I

STUDY GROUPS						
Gender	**Case**		**Control**		**Total**	
	n	%	n	%	N	%
Male	36	53.7	37	56.9	73	55.3
Female	31	46.3	28	43.1	59	44.7
Total	67	100.0	65	100.0	132	100.0

***X^2** value = 0.136. P = 0.712. *Not Significant* (P > 0.05)

Table II

STUDY GROUPS						
AGE IN GROUPS	**Case**		**Control**		**Total**	
	n	%	n	%	N	%
> 60 Years	23	34.3	14	21.5	37	28.0
≤ 60 Years	44	65.7	51	78.5	95	72.0
Total	67	100.0	65	100.0	132	100.0

***X^2** value = 2.675. P = 0.102.

Table III

STUDY GROUPS								
Risk Factors		**Case**		**Control**		**Total**		**X^2** Test Significance
		n	%	n	%	n	%	
Diabetes Mellitus	Present	09	13.4	06	9.2	15	11.4	$X^2 = 0.578$ $P = 0.447^{NS}$
	Absent	58	86.6	59	90.8	117	88.6	
Hypertension	Present	50	74.6	10	15.4	60	45.5	$X^2 = 46.703$ $P = 0.000^{HS}$
	Absent	17	25.4	55	84.6	72	54.5	
Cigarette Smoking	Present	21	31.3	09	13.8	30	22.7	$X^2 = 5.751$ $P = 0.016^{S}$
	Absent	46	68.7	56	86.2	102	77.3	
Obesity	Present	09	13.4	06	9.1	15	11.4	$X^2 = 0.578$ $P = 0.447^{NS}$
	Absent	58	86.6	59	90.8	117	88.6	
Low Cholesterol	Present	50	74.6	21	32.3	71	53.8	$X^2 = 23.771$ $P = 0.000^{HS}$
	Absent	17	25.4	44	67.7	61	46.2	

* NS = Not Significant (P > 0.05); S = Significant (P < 0.05)

HS = Highly Significant (P < 0.001)

Table IV

Serum Biochemical Variables	Study Groups	N	MEAN	± SD	MEDIAN	RANGE	SIGN.*
SerumTotal	Case	67	180.36	49.38	172.00	107 – 347	**t** = 4.602
Cholesterol	Control	65	217.68	43.50	210.00	110 – 329	P =0.000
(mg/dL)	TOTAL	132	198.73	50.04	193.50	107 – 347	
Serum	Case	67	106.63	40.69	98.00	46 – 270	**t** = 3.89
LDL	Control	65	128.57	35.71	130.00	40 – 239	P = 0.001
(mg/dL)	TOTAL	132	117.43	39.73	115.00	40 – 270	
Serum	Case	67	43.84	11.75	42.00	16 – 89	**t** = 0.190
HDL	Control	65	44.15	6.91	43.00	30 – 62	P = 0.850
(mg/dL)	TOTAL	132	43.99	9.64	43.00	16 – 89	
Serum	Case	67	115.23	51.65	109.00	43 – 350	**t** = 4.376
TG	Control	65	187.43	121.88	154.00	62 – 820	P = 0.000
(mg/dL)	TOTAL	132	150.80	99.48	123.00	43 – 820	

Independent samples t-test. HS = Highly Significant (P < 0.001); NS = Not Significant (P > 0.05)

Table V

Risk factors of stroke	*OR*	*95% confidence interval*	*P value*
Diabetes Mellitus	1.62	0.30-8.66	0.56
CigaretteSmoking	1.64	0.53-5.03	0.45
Obesity	1.80	0.38-8.45	0.557
Hypertension	18.08	6.50-50.2	0.001
Age>60	2.45	0.79-7.3	0.018
Low Cholesterol	6.03	2.1-16.5	0.001

In the present study, among the total 132 subjects, 55.3% were male and 44.7% were female and ratio between male and female was 1.2:1. Presently in our socioeconomic condition, males get more attention than females and are taken to and treated in the hospitals more. So the present finding regarding gender distribution is consistent with our social architecture and it is likely that this does not represent the real percentage of incidence of ICH among women of our country.

We found DM was mildly associated with ICH but statistically insignificant (OR 1.62, p>0.05). DM was defined as patients with history with DM or taking anti diabetic medications and by Capillary Blood Glucose (CBG) analysis. In one study role of diabetes mellitus in the pathogenesis of intracerebral hemorrhage (ICH) is controversial[12]. We also found obesity was mildly associated with ICH but statistically insignificant (OR 1.80, p>0.05). Obesity was calculated from Body Mass Index (BMI). The present study found cigarette smoking to be statistically insignificant (OR= 1.64; p>0.05). In previous studies, some found positive association between cigarette smoking and primary ICH[13]. Whereas, some studies did not find any association between smoking and ICH.[14]

74.6% of the patients were hypertensive in our study and hypertension was found to be the commonest major risk factor in hemorrhagic stroke (OR=18.08; CI 6.50-50.2; p=0.0001). This study defined Hypertension was defined as patients having history of hypertension with or without taking antihypertensives. Hypertension as the number one risk factor was also found in other studies.[15,16,17] In those studies hypertension was found in 59.09%, 68.30% and 60% of patients respectively, which are relatively less than our finding. But in another study of 188 patients with primary ICH, hypertension was observed in 72% of the patients, which corresponds with our study.[18]

Serum total cholesterol was found significantly low in the case group than in the control group (P<0.001). Mean total cholesterol was 180.36 mg/dl in case group and 217.68 mg/dl in control group. Although mean total cholesterol was significantly low in both young and elderly individuals, the difference was statistically significant in individuals above 60 years of age (OR=2.45; CI 0.79-7.3; p=0.018). In the largest population-based study MRFIT,[19] the mean cholesterol level in the hemorrhage and non-hemorrhage groups was 211 ± 14 and 214 ± 40, respectively, with a pronounced increase in hemorrhage only among those with cholesterol <160 mg/dl.

Corroborating previous findings examining ICH and cholesterol, we observed an inverse association between LDL-c and ICH. Mean LDL-c was 106.63 mg/dl in case group and 128.57 in control group (p<0.05).

An Indian study found the proportion of ICH patients with low cholesterol was significantly higher than controls (68%

vs. 43%). Mean total cholesterol was also significantly low in ICH patients compared with controls (177 mg/dl vs. 200 mg/dl, p=.0006).[20] LDL-c and TG were also significantly low in ICH patients compared with controls. Although lower mean cholesterol was seen in both young and older individuals in ICH groups than in controls, the difference was significant only in older group (Age.45 years). The odds ratio of low cholesterol in hemorrhage cases was 2.75 (95% CI 1.44-5.49). Our study is similar to this study. A Turkish study also found mean cholesterol level of patients to be significantly lower than the controls ($p<0.05$). In ICH group, frequency of patients who had the very low cholesterol levels was significantly higher than the control group ($p<0.05$).[21] Results of both the studies are similar to our study.

From this study, our inference is that, older age, hypertension, low total cholesterol, low LDL-c and low TG increase the risk of ICH. So in our context, low level of cholesterol and hypertension are two important modifiable risk factors for the development of hemorrhagic stroke.

Conclusion: Along with other risk factors like hypertension and old age, low total cholesterol also plays an important role for development of primary intracerebral hemorrhage. Present study found significant association with low total cholesterol with primary intracerebral hemorrhage specially in older population. This finding of relationship between serum lipids and primary intracerebral hemorrhage has implication for both prevention of intracerebral hemorrhage as well as the potential risk of lipid lowering therapies.

References:

1. Roquer J, Campello AR, Gomis M, Ois A, Munteis E, Böhm P. Serum lipid levels and in-hospital mortality in patients with intracerebral hemorrhage. Neurology. 2005; 65(8):1198-202.
2. Tanaka H, Ueda Y, Hayashi M, Date C, Baba T, Yamashita H. et al. Risk factors for cerebral hemorrhage and cerebral infarction in a Japanese rural community. Stroke. 1982 1;13(1):62-73.
3. Lecerf JM, De Lorgeril M. Dietary cholesterol: from physiology to cardiovascular risk. British Journal of Nutrition. 2011;106(1):6-14.
4. Yano K, Reed DM, MacLean CJ. Serum cholesterol and hemorrhagic stroke in the Honolulu Heart Program. Stroke. 1989 ;20(11):1460-5.
5. Hu HH, Sheng WY, Chu FL, Lan CF, Chiang BN. Incidence of stroke in Taiwan. Stroke. 1992;23(9):1237-41.
6. Konishi M, Iso H, Komachi Y, Iida M, Shimamoto T, Jacobs DR et al. Associations of serum total cholesterol, different types of stroke, and stenosis distribution of cerebral arteries. The Akita Pathology Study. Stroke. 1993 ;24(7):954-64.
7. Bruckdorfer KR, Demel RA, De Gier J, Van Deenen LL. The effect of partial replacements of membrane cholesterol by other steroids on the osmotic fragility and glycerol permeability of erythrocytes. Biochimica et Biophysica Acta (BBA)-Biomembranes. 1969;183(2):334-45.
8. Ooneda G, Yoshida Y, Suzuki K, Shinkai H, Hori S, Kobori K et al. Smooth muscle cells in the development of plasmatic arterionecrosis, arteriosclerosis, and arterial contraction. Journal of Vascular Research. 1978;15(1-3):148-56.
9. Takeya Y, Popper JS, Shimizu Y, Kato H, Rhoads GG, Kagan A. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: incidence of stroke in Japan and Hawaii. Stroke. 1984 ;15(1):15-23.
10. Muldoon MF, Manuck SB, Matthews KA. Lowering cholesterol concentrations and mortality: a quantitative review of primary prevention trials. Bmj. 1990;301(6747):309-14
11. Alam B, Habib H, Qurashi FA, Badrul H, Haque A, Mohammed QD. Stroke-Evaluation of risk factors. Bangladesh Journal of Neuroscience. 1999;15(1/2):14-18.
12. Hesami O, Kasmaei HD, Matini F, Assarzadegan F, Mansouri B, Jabbehdari S. Relationship between intracerebral hemorrhage and diabetes mellitus: a case-control study. Journal of clinical and diagnostic research: JCDR. 2015;9(4): OC08-10.
13. Abbott RD, Curb JD, Rodriguez BL, Masaki KH, Yano K, Schatz IJ et al. Age-related changes in risk factor effects on the incidence of coronary heart disease. Annals of epidemiology. 2002;12(3):173-81.
14. Fogelholm R, Murros K. Cigarette smoking and risk of primary intracerebral haemorrhage. Actaneurologicascandinavica. 1993;87(5):367-70.
15. Rahman M, Musarrof AK, Patwary I. Risk factor of strokes-a clinical study. Bangladesh J Med. 2000;2:90-4.
16. Chowdhury MNH. Effect of Levodopa in Combination with Task Specific Training on Functional Motor Recovery after Stroke. Thesis 2003. Page 68-70 and appendix – I (BSMMU; Department of Neurology).
17. Bhuiyan M, Rahman HZ, Islam MR. Four year Evaluation of Stroke Patient in Stroke Clinic. Bangladesh Journal of Neuroscience. 2004; 20:50-4.
18. Mazziotta JC, Fenichel GM, Daroff RB, Jankovic J. Bradley's Neurology in Clinical Practice. Elsevier Health Sciences; 2012.6th edition, Elsevier Sanders, 2012:pp-1054-1066.
19. Iso H, Jacobs Jr DR, Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. New England Journal of Medicine. 1989;320(14):904-10.
20. Valappil AV, Chaudhary NV, Praveenkumar R, Gopalakrishnan B, Girija AS. Low cholesterol as a risk factor for primary intracerebral hemorrhage: A case–control study. Annals of Indian Academy of Neurology. 2012;15(1):19.
21. Orken DN, Kenangil G, Celik M, Mail Z, Kayaalp H, Erginoz E et al. Association of low cholesterol with primary intracerebral haemorrhage: a case control study. ActaNeurologicaScandinavica. 2009;119(3):151-4.