

Association of low serum cholesterol levels with increased risk of primary intracerebral hemorrhage

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Objective Several of the risk factors that increase the risk of primary intracerebral hemorrhage (PICH) are well documented. However, the association between serum cholesterol levels and PICH is still controversial. The objective of this study was to evaluate the correlation between serum cholesterol levels and PICH in Thai people.

Methods In this retrospective case-control study, the serum cholesterol levels in PICH patients were compared to an independent control group in a primary care practice hospital in patients having yearly health check ups during the study. Participants were matched for age, gender, and race. The lowest quartile of the pooled blood lipid distribution was designated as the low cholesterol threshold.

Results From 2015 to 2016, 55 cases of PICH and 112 control cases were enrolled. The mean total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) level in the PICH group was significantly lower than the control group (TC 176 mg/dL vs 211 mg/dL, $p < 0.001$; LDL-C 107.2 mg/dL vs 145 mg/dL, $p < 0.001$, respectively). A low LDL-C also increases the odds of hemorrhage by 11.78-fold (3.78-36.67, $p < 0.001$) after adjustment for covariates.

Conclusions Low serum TC and LDL-C levels are associated with an increased risk of PICH in Thai people. **Chiang Mai Medical Journal 2018;57(4):165-71.**

Keywords: risk factors, primary intracerebral hemorrhage, cholesterol, Thai

Introduction

Cerebrovascular disease or stroke is a significant public health issue in most countries. The number of disabilities and deaths due to strokes are continuously rising due to the aging of populations. Ten to fifteen percent of all strokes are caused by intracerebral hemorrhage (ICH), and 85% are considered to be primary intracerebral hemorrhage (PICH) (1). Even with the best medical or surgical treatment, the 30-day mortality rate is still as high

as 35-52% (2). Hence, identification of modifiable risk factors is crucial for disease prevention.

Several risk factors for PICH, including old age, hypertension (HTN), cerebral amyloid angiopathy (CAA), and alcohol consumption are well documented (3-5). However, the ideal level of serum cholesterol is still controversial. While hyperlipidemia has been demonstrated to be a risk factor for cardiovascular disease

and ischemic stroke, a low cholesterol level has been found to increase the risk of PICH in many population-based studies done in various countries.

In addition, the 3-hydroxy-3-methyl glutaryl-coenzyme A (HMG-CoA) reductase inhibitors or statins, which primarily reduce serum levels of TC and LDL-C, are widely used and have achieved favorable outcomes for both primary and secondary prevention in ischemic stroke patients (6-9). In post hoc analysis, however, a stroke prevention by aggressive reduction in cholesterol level trial (SPARCL trial) demonstrated that atorvastatin was associated with an increased risk of PICH (8,10). This controversy may affect secondary prevention strategies and the use of lipid-reducing drugs in PICH patients (11-17).

In Thailand, no study has reported an association between serum cholesterol and the risk of PICH. This study tested the hypothesis that low serum cholesterol levels might be associated with PICH and investigated the relationship between different categories of cholesterol and the risk of PICH.

Methods

The protocol for this retrospective case-control study was approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University. The study was conducted with the informed consent of all participants or their guardians.

One hundred and fifty-five consecutive adult patients admitted to Maharaj Nakorn Chiang Mai Hospital, Chiang Mai, Thailand from January 2015 through December 2015 with a diagnosis of ICH were enrolled in this study. The diagnosis of ICH was defined as a sudden onset of an acute neurological event with confirmation of acute intraparenchymal hematoma shown on brain computed tomography (CT) scans. Of 155 cases, a total of 55 patients were considered as having PICH after excluding patients who had had a prior cerebrovascular accident (n=16); secondary ICH related to aneurysm (n=13), arteriovenous malformations (n=11), trauma (n=11) or tumors (n=14), excessive anticoagulation (international normalized ratio>1.3), or who had received anticoagulant therapy (n=12). Because of the effect of diabetes on lipid levels, patients requiring diabetes medication (insulin or oral hypoglycemic agent (n=23) were also excluded.

The control group consisted of 112 individuals who presented to a primary care clinic for a routine check-up examination without a prior cerebrovascular accident and who did not require diabetes medication treatment during the study period. The patient and control groups were matched for age, sex, and race. A flow chart summarizing inclusion and exclusion criteria is shown in Figure 1.

All patients were Thai and each patient's history, physical examination, baseline characteristics including age, sex, presence of hypertension (defined as pre-hemorrhage blood pressure documented to be >140 mmHg systolic or >90 mmHg diastolic or use of an anti-hypertensive agent), and use of statins were recorded.

For the patient group, serum lipid profiles were obtained after eight or more hours of fasting within 48 hours of an acute vascular event and were reported in mg/dL. TC, high density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels were measured in serum by standard chemical methods and the LDL-C levels were calculated using the Friedewald formula.

Statistical analysis

The low serum lipid threshold (TC <186mg/dL, HDL-C<40mg/dL, LDL-C<109.7mg/dL, TG <83 mg/dL) was designated as the lowest quartile based on the pooled blood lipid distribution as described in a study by Sturgeon et al. (18). The proportion of individuals with low cholesterol and TG in the PICH and the control group was compared using 2x2 tables using Fisher's exact test to determine statistical significance. Demographic data, cholesterol levels, and TG values of PICH patients and controls were compared using either the t-test or the Mann-Whitney U test. All the significance tests were two-sided, with $p<0.05$ designated as statistically significant unless stated otherwise. All confidence intervals (CI) were set at 95%. Multivariate logistic regression analysis was performed. The potential covariates examined were hypertension and statin use. All analyses were performed using Stata software.

Results

A total of 55 patients and 112 healthy controls were enrolled in this study. The demographic data is summarized in Table 1. The mean age was 57.7 ± 14.1 years for patients and 58.4 ± 12.7 years for controls. Forty-five patients (81.8%) and eighty-three controls (74.1%) were male. There were no significant differences in the distribution of age, sex, or statin use between the two groups. However, the frequency of hypertension was significantly

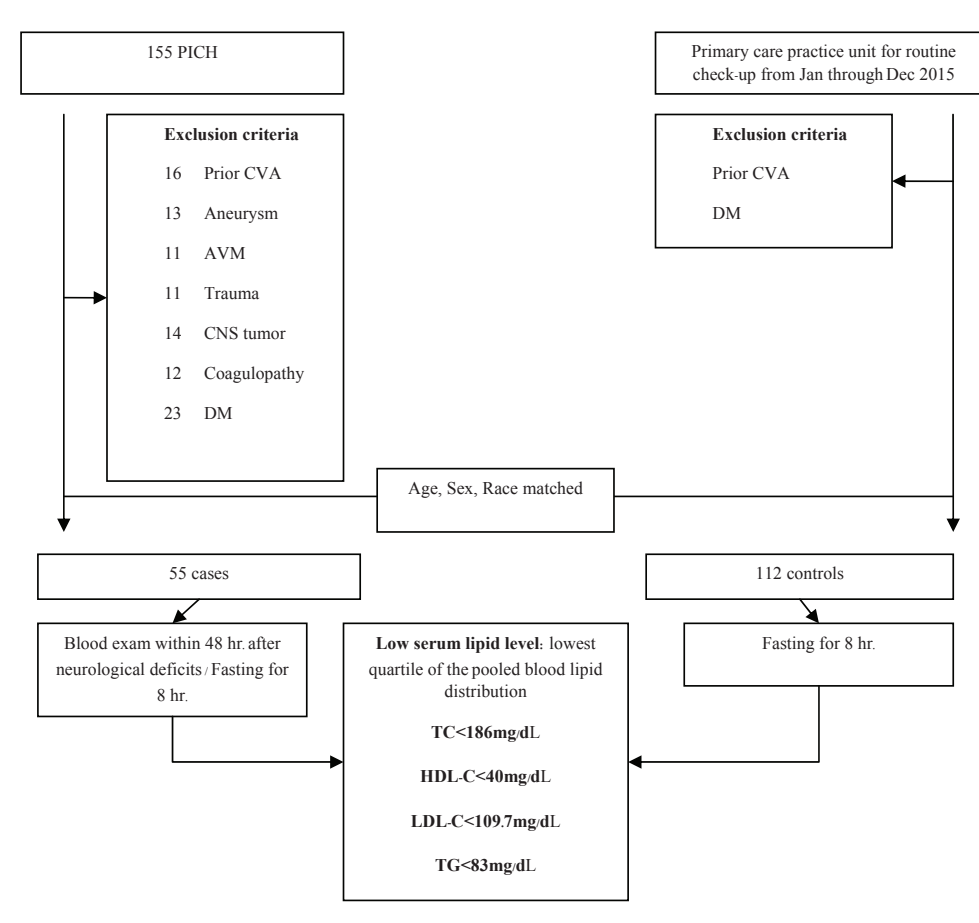


Figure 1. Flow chart of inclusion and exclusion criteria

Table 1. Demographic data in patients with primary intracerebral hemorrhage (PICH) and controls

Characteristics	PICH patients (n=55)	controls (n=112)	p-value
Age in years	57.7 ±14.1	58.4±12.7	0.756
Sex, male/female	45 (81.8%)/10 (18.2%)	83 (74.1%)/29 (25.9%)	0.332
Hypertension	29 (52.7%)	29 (25.9%)	0.001
Statin use	2 (3.6%)	10 (8.9)	0.340

higher in the patients than in the control group, (57% vs 25.9%, $p=0.001$).

The mean TC and LDL-C levels in patients were significantly lower than in the control group (TC 176 mg/dL vs 211mg/dL, $p<0.001$; LDL-C 107.2mg/dL vs 145.4, $p<0.001$, respectively). There were no significant differences in HDL-C or TG in mean analysis between patients and controls (Table 2).

A significantly higher proportion of patients had TC and LDL-C values in the lowest quartile compared to controls. Lower TC values (below 186 mg/dL) were found in 60% of the

patients and 27.7% of the control group ($p<0.001$); lower LDL-C (below 109.7 mg/dL) was found in 56.4% of the patients and 11.6% of the control group ($p<0.001$).

Multivariate analysis was performed to control for potential covariates of cholesterol such as hypertension and prior use of statin. The presence of low LDL-C remained a significant predictor of hemorrhage. The odds ratio of low LDL-C in the hemorrhage patients was 9.84 (95% CI=4.48-21.59) unadjusted and 11.78 (95% CI=3.78-36.67) after adjusting for hypertension and prior use of statins (Table 3).

Table 2. Serum lipid levels in patients with primary intracerebral hemorrhage (PICH) and controls

Serum lipid level	PICH patients (n=55)	controls (n=112)	p-value
TC			
Mean $\pm$ SD (mg/dL)	176 $\pm$ 51.6	211 $\pm$ 40.2	<0.001
< 186 mg/dL, n (%)	33 (60.0)	31 (27.7)	<0.001
HDL-C			
Mean $\pm$ SD(mg/dL)	49.7 $\pm$ 14.6	53.9 $\pm$ 14.8	0.085
< 40 mg/dL, n (%)	15 (27.3)	14 (12.5)	0.028
LDL-C			
Mean $\pm$ SD(mg/dL)	107.2 $\pm$ 44.2	145.4 $\pm$ 31.6	<0.001
< 109.7 mg/dL, n (%)	31 (56.4)	13 (11.6)	<0.001
TG			
Median (range) (mg/dL)	105 (41-1480)	119 (49-400)	0.352
< 83 mg/dL, n (%)	17 (30.9)	27 (24.1)	0.356

TC; total cholesterol, HDL-C; high density lipoprotein cholesterol, LDL-C; low density lipoprotein cholesterol, TG; triglyceride

Table 3. Logistic regression analysis of the association of low serum lipid fraction and PICH

Factors	Univariate analysis of factors for PICH			Multivariate analysis of factors for PICH		
	OR	95% CI	p-value	OR	95% CI	p-value
Hypertension	3.19	1.62 to 6.29	0.001	4.35	1.88 to 10.03	0.001
Statin use	0.38	0.08 to 1.82	0.229	0.11	0.02 to 1.47	0.203
TC <186 mg/dL	3.92	1.99 to 7.74	<0.001	1.21	0.44 to 3.32	0.706
HDL-C <40 mg/dL	2.63	1.16 to 5.94	0.020	0.92	0.32 to 2.65	0.880
LDL-C <109.7 mg/dL	9.84	4.48 to 21.59	<0.001	11.78	3.78 to 36.67	<0.001
TG < 83 mg/dL	1.41	0.69 to 2.89	0.349	0.63	0.23 to 1.76	0.378

TC; total cholesterol, HDL-C; high density lipoprotein cholesterol, LDL-C; low density lipoprotein cholesterol, TG; triglyceride

Discussion

Thai patients with PICH had an average age of 57.7 years and were predominantly male (45 cases, 81.8%). Hypertension in PICH patients was significantly higher than in the control group (57.2% vs 25.9%, $p=0.001$) with an odds ratio of 3.19 (95% CI=1.62-6.29, $p=0.001$). This study confirmed that hypertension is a consistent risk factor for PICH.

In this study, we found that TC and LDL-C levels were significantly lower in the patient group compared to the control group. However, the HDL-C and TG levels were not significantly different between the two groups. The proportion of PICH patients who had TC and LDL-C levels in the lowest quartile was also higher than that of the control group. This finding is in concordance with large epidemiological studies

in other Asian countries such as Japan, China, Korea, and India, and even among several Western countries (19-25).

Pathology studies in PICH patients with chronic hypertension have shown hyperplasia of the tunica media in the small artery walls that eventually resulted in fibrinoid necrosis. Lipids are essential components of the cell membrane and play an important role in maintaining the stability of endothelial cells and the integrity of cerebral small vessels. It has been proposed that lower cholesterol levels result in a weakened endothelium that more readily leads to arterial fragility, hemorrhages, or slower repair after small hemorrhages. However, it remains unclear whether low cholesterol directly promotes ICH through these or other mechanisms.

Although statin therapy has been shown to reduce the risk of ischemic stroke, its use in PICH patients is still controversial. Because statins can reduce platelet aggregation and have antithrombotic effects, some authors suggest avoiding statin therapy in PICH (26,27). Nonetheless, other studies designed specifically to assess the effect of statin use after ICH found statins to be safe and to have even improved functional outcomes (17, 28-31). The author suggests that until a well-designed randomized controlled trial has been conducted, statin therapy in PICH patients should be considered carefully and closely monitored.

Several limitations in this study should be addressed. First, a potential source of error in this study is the use of serum lipid levels during the first 48 hours after ICH as an estimate of pre-hemorrhage levels. Some studies carried out following strokes have reported that cholesterol levels decline in the first 24-48 hours after a stroke (32). Flint et al (30) studied the cholesterol levels in a smaller group of PICH patients and found TC to be lower after one week than within 48 hours of hemorrhage. They concluded that lipid profiles should be assessed either within 48 hours of stroke onset or delayed for three months to avoid inaccurate measurement (33). A second limitation is that since PICH patients who were admitted to the hospital and enrolled in this study were those who had survived the onset of PICH, a survival bias might exist. Furthermore, as the largest teaching hospital in Chiang Mai, Thailand, patients with more critical conditions tend to be admitted to this hospital, which may have lead to the introduction of selection bias.

Conclusions

Low total and LDL cholesterol levels are associated with an increased risk of PICH. Clinicians should be aware of the risk of PICH in hypertensive patients with very low cholesterol levels. The use of cholesterol-lowering drugs must be carefully prescribed and regularly monitored. Because of the complex pathogenesis of PICH, however, we are still unable to claim that this relationship is a causative factor of PICH. Further investigation is warranted to answer that question.

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ความสัมพันธ์ระหว่างระดับคอเลสเตอรอลในเลือดต่ำกับการเพิ่มความเสี่ยงภาวะเลือดออกในเนื้อสมอง

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วัตถุประสงค์ ความเสี่ยงของภาวะเลือดออกในเนื้อสมองมีหลายปัจจัย แต่อย่างไรก็ตามความสัมพันธ์ระหว่างระดับของคอเลสเตอรอลในเลือดต่ำเป็นปัจจัยเสี่ยงต่อภาวะเลือดออกในเนื้อสมองนั้นยังไม่เป็นที่ปรากฏแน่ชัด ดังนั้นวัตถุประสงค์ของการศึกษานี้คือศึกษาความสัมพันธ์ระหว่างระดับคอเลสเตอรอลในเลือดต่ำกับการเกิดภาวะเลือดออกในเนื้อสมองในกลุ่มตัวอย่างคนไทย

วิธีการศึกษา ทีมผู้วิจัยได้ทำการศึกษาย้อนหลัง case-control study อาศัยตัวแปรจากระดับคอเลสเตอรอลในเลือดของผู้ป่วยภาวะเลือดออกในเนื้อสมอง นำมาเปรียบเทียบกับระดับคอเลสเตอรอลในเลือดของกลุ่มควบคุมอิสระที่มีอายุ เพศและเชื้อชาติเดียวกันกับผู้ป่วยที่ได้รับการตรวจสุขภาพประจำปีในช่วงระยะเวลาการศึกษาเดียวกัน

ผลการศึกษา ระหว่างปี พ.ศ. 2558-2559 มีผู้ป่วยภาวะเลือดออกในเนื้อสมองเข้าร่วมวิจัยจำนวน 55 ราย และกลุ่มควบคุม จำนวน 112 ราย ผลพบว่าระดับ total cholesterol (TC) และ low density lipoprotein cholesterol (LDL-C) ในกลุ่มผู้ป่วยภาวะเลือดออกในเนื้อสมองมีค่าน้อยกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ (TC 176 มก./ดล. vs 211 มก./ดล., $p < 0.001$; LDL-C 107.2 มก./ดล. vs 145 มก./ดล., $p < 0.001$ ตามลำดับ) อีกทั้งหลังจากที่ได้การปรับอิทธิพลของตัวแปรอื่น ระดับ LDL-C ต่ำ ยังเป็นปัจจัยเสี่ยงที่เพิ่มอัตราการเกิดภาวะเลือดออกในเนื้อสมอง 11.78 เท่า (3.78-36.67, $p < 0.001$)

สรุป ในการศึกษาในกลุ่มตัวอย่างคนไทยระดับค่า TC และค่า LDL-C ที่มีค่าต่ำมีความสัมพันธ์ในการเพิ่มความเสี่ยงการเกิดภาวะเลือดออกในเนื้อสมอง **เชียงใหม่เวชสาร 2561;57(4):165-71.**

คำสำคัญ: ปัจจัยเสี่ยง ภาวะเลือดออกในเนื้อสมอง ระดับคอเลสเตอรอล คนไทย