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Higher low-density lipoprotein cholesterol levels are associated with decreased mortality in patients with intracerebral hemorrhage

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ABSTRACT

Background and aims: The relationship between lipoprotein levels, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and clinical outcome after intracerebral hemorrhage (ICH) remains controversial. We sought to evaluate the association of lipoprotein cholesterol levels and statin dosage with clinical and neuroimaging outcomes in patients with ICH.

Methods: Data on consecutive patients hospitalized with spontaneous acute ICH was prospectively collected over a 5-year period and retrospectively analyzed. Demographic characteristics, clinical severity documented by NIHSS-score and ICH-score, neuroimaging parameters, pre-hospital statin use and doses, and LDL-C and HDL-C levels were recorded. Outcome events characterized were hematoma volume, hematoma expansion, in-hospital functional outcome, and in-hospital mortality.

Results: A total of 672 patients with acute ICH [(mean age 61.6 ± 14.0 years, 43.6% women, median ICH score 1 (IQR: 0–2)] were evaluated. Statin pretreatment was not associated with neuroimaging or clinical outcomes. Higher LDL-C levels were associated with several markers of poor clinical outcome and in-hospital mortality. LDL-C levels were independently and negatively associated with the cubed root of hematoma volume (linear regression coefficient −0.021, 95% CI: −0.042–-0.001; $p = 0.049$) on multiple linear regression models. Higher admission LDL-C (OR 0.88, 95% CI 0.77–0.99; $p = 0.048$) was also an independent predictor for decreased hematoma expansion. Higher admission LDL-C levels were independently ($p < 0.001$) associated with lower likelihood of in-hospital mortality (OR per 10 mg/dL increase 0.68, 95% CI: 0.57–0.80) in multivariable logistic regression models.

Conclusions: Higher LDL-C levels at hospital admission were an independent predictor for lower likelihood of hematoma expansion and decreased in-hospital mortality in patients with acute spontaneous ICH. This association requires independent confirmation.

1. Introduction

The relationship between lipoprotein cholesterol levels [low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C)] and clinical outcomes in patients with acute intracerebral hemorrhage (ICH) remains controversial. Early epidemiological studies suggested an association between lower cholesterol levels and death after stroke [1]. Subsequent studies further evaluated LDL-C with associations noted between lower LDL-C levels and ICH risk [2], hematoma growth [3], and mortality [4–6].

As the primary agent responsible for lowering lipid levels, the role of statins in ICH incidence and hematoma volume expansion has generated controversy. This was particularly highlighted after statins were found to be associated with increased rates of hemorrhagic transformation in ischemic stroke [7] and higher incidence of cerebral microbleeds in ICH [8]. However, recent studies have

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also provided observational evidence showing statin use improving clinical outcomes after ICH [9,10] and not increasing the likelihood of cerebral microbleeds [11].

The relationship between statin use and dosing, lipoprotein levels, hematoma volume, and clinical outcome remains unclear due to inconsistencies in the existing literature and failure to systematically evaluate both clinical and neuroimaging outcomes in individual patients. To clarify this relationship, we sought to evaluate the association of lipoprotein cholesterol levels with clinical and neuroimaging outcomes in patients with acute ICH.

2. Materials and methods

2.1. Patient selection and study protocol

Institutional review board approval was obtained for the conduct of a prospective cohort study evaluating functional and neuroimaging outcomes in adult patients with acute, spontaneous, non-traumatic ICH in a tertiary-care stroke center. All data was prospectively collected as per hospital registry protocol for acute (<24 h) ICH and retrospectively reviewed for accuracy by blinded neurologists (YK, KD, AK, NG). Consecutive patients with ICH were initially identified by ICD code, which spanned a five-year period (from January 2011 to December 2015). Inclusion criteria were as follows: spontaneous etiology for ICH and adult age ($\geq$18 years old). Exclusion criteria were as follows: nonspontaneous etiologies of ICH (including traumatic ICH, metastatic lesion with associated hemorrhage, ICH resulting from venous sinus thrombosis, and ICH resulting from underlying vascular lesions), ICH due to supratherapeutic international normalized ratio (INR) in the setting of prehospital anticoagulation or coagulopathy (threshold INR $\geq$ 1.7), and thrombocytopenia (platelets < 50,000/mm^3).

All ICHs were initially admitted to the intensive care unit (ICU). As per hospital protocol, patients were treated with intravenous pushes of enalapril, hydralazine, or labetalol and escalated to continuous nicardipine infusion to reach a goal SBP <140 mmHg during the first 24 h after admission. If clinically stable, SBP parameters were relaxed to SBP goal <160 mmHg after 24 h of admission. As per hospital protocol and unless contraindicated or on a different prehospital statin dose, all patients with ICH were given a medium-dose statin within 24 h of admission after swallow evaluation or feeding tube insertion. Intensive statin pretreatment was defined as patients taking the maximum dose of their respective statin [12].

Demographic characteristics, past medical history, premorbid modified Rankin scores (mRS), and baseline radiological and clinical parameters were prospectively collected. Baseline clinical severity was documented with National Institutes of Health Stroke Scale (NIHSS) scores. Clinical outcome endpoints included mRS at discharge, hospital length of stay, and in-hospital mortality. Favorable functional outcome at discharges was defined as mRS 0–2. All laboratory values—INR, glucose, platelets, LDL-C, HDL-C—were obtained within 24 h of hospitalization.

2.2. Mortality analysis

Causes of mortality were delineated as follows. Cerebral herniation occurred when the patient reached a comatose state from herniation, was not formally declared brain dead, and passed away from cardiac death after palliative extubation. Brain death occurred when patients met clinical criteria which included loss of brainstem reflexes and apnea testing confirmation or ancillary testing for cerebral circulatory arrest. Spontaneous cardiac arrest occurred during an unanticipated cardiac arrest, unrelated to their primary ICH. Finally, palliative care occurred when the patient remained extubated for longer than 24 h and was transitioned to comfort measures with subsequent death.

2.3. Imaging characterization: ICH volume, and hematoma expansion

Follow-up head computed tomography (CTH) was acquired within 6–24 h of initial CTH. ICH volume as noted in baseline CTH was measured as delineated by the ABC/2 score [13]. Hematoma expansion was defined as >33% expansion or >12.5 ml hematoma volume growth on serial CT scans taken within a 48-h span [14–16].

2.4. Statistical analysis

We presented continuous parametric data using their mean values together with their corresponding standard deviations (SDs). We used median values with their corresponding interquartile ranges (IQR) for the presentation of non-parametric data and percentages for all dichotomous variables.

Univariate and multivariate regression analyses were used to evaluate the associations between baseline characteristics and admission hematoma volume, hematoma expansion, functional dependence at hospital discharge (mRS scores 3–6), in-hospital mortality among included patients. In all univariate analyses, a threshold of $p < 0.1$ was used to identify candidate variables for inclusion in multivariate regression models that tested statistical significance hypothesis using the likelihood ratio test with an alpha value of 0.05 [17]. We reported all associations as linear regression coefficients in linear regression models and odds ratios (ORs) in logistic regression models, respectively, with their corresponding 95% confidence intervals (95% CI). In all simple and multiple linear regression analyses, baseline hematoma volume was cube root transformed for each patient to satisfy statistical assumptions regarding normality of the distribution, as previously described [18]. The Stata Statistical Software Release 13 for Windows (College Station, TX, StataCorp LP) was used for all statistical analyses.

3. Results

A total of 803 patients were identified as ICH by ICD code; of these patients, 672 met inclusion criteria [mean age 61.6 ± 14.0 years, 43.6% women, median ICH score 1 (IQR: 0–2)]. Baseline characteristics for the study population are included in Table 1. Statin pretreatment was documented in 25.8% and intensive pretreatment statin was documented in 3.4% of the study population (mean admission LDL-C: 100.3 ± 36.3 mg/dl; mean admission HDL-C: 52.6 ± 18.6 mg/dl).

Associations between demographic variables and the cubed root of hematoma volume at admission are shown in Table 2. Several demographic variables were associated with cubed root of hematoma volume on simple linear regression analysis: Caucasian race, history of hypertension, history of hyperlipidemia, coronary artery disease, past history of stroke, admission glucose, admission LDL-C, subcortical location for ICH, admission systolic blood pressure (SBP), and admission NIHSS. Admission LDL-C levels were found to be negatively correlated with admission hematoma volumes (Fig. 1). Multiple linear regression analyses identified the following independent predictors of admission hematoma volume: history of stroke, admission LDL-C, subcortical location of ICH, and admission NIHSS. More specifically, LDL-C levels ($p = 0.049$) were independently and negatively associated with the cubed root of hematoma volume (linear regression coefficient: 0.021, 95% CI -0.042 to −0.001) on hematoma volumes after adjusting for potential confounders.

The following variables were related to hematoma expansion on