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Oral contraceptive use and incident stroke in women with sickle cell disease

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ABSTRACT

Objective: Oral contraceptives increase the risk of ischemic stroke among women. However, the effect is not studied in the stroke prone sickle cell disease (SCD) population. We want to determine the rate of incident stroke among women with SCD enrolled in a large cohort with longitudinal follow-up.
Study Design: A total of 1257 women aged ≥15 and <45 years, enrolled in Phase 1 of Cooperative Study of SCD, underwent a baseline examination for assessment of demographics, prior medical history, laboratory assessments, and clinical data. The effects of active oral contraceptive use at baseline interview on incident ischemic and hemorrhagic strokes were assessed after adjusting for potential confounders using Cox Proportional Hazards analysis.
Results: A total of 178 (14.2%) of 1257 women with SCD reported use of oral contraceptives. The age adjusted annual incidence of incident stroke was four folds higher among women who reported active oral contraceptive use than those who did not report use (1.6/100 person-years versus 0.4/ 100 person-years, $p = 0.03$). After adjusting for age, cigarette smoking status, history of exchange transfusions, alcohol use, body weight, systolic blood pressure, and heart rate, oral contraceptive use was not significantly associated with rate of ischemic stroke (hazards ratio [HR], 3.6 95% confidence interval [CI] 0.8-16.5, $p = 0.09$) or hemorrhagic stroke (HR, 1.2 95% CI 0.2-5.7, $p = 0.8$).
Conclusions: The four fold higher risk of incident stroke associated with use of oral contraceptives in women with SCD can be mitigated by controlling other cardiovascular risk factors.
Implications: Our results are expected to increase the awareness, among both medical practitioners and patients, regarding the four fold higher risk of incident stroke associated with use of oral contraceptives in women with SCD. Our results also identify the confounding effect of other cardiovascular risk factors such as cigarette smoking on the observed relationship and thus identify potential targets for prevention.

Introduction

Women with sickle cell disease (SCD) are at risk for ischemic and hemorrhagic stroke at a rate higher than observed in general population [1–6]. A population-based study determined that the rate of stroke associated with SCD was highest in older adults and was three-fold higher than rates previously reported in persons without SCD [7]. The study also identified the role of modifiable risk factors for stroke such as hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, and renal disease in adults with SCD. Oral contraceptive use is associated with a higher risk of ischemic and hemorrhagic stroke in healthy women [8,9]. However, the increased risk of ischemic stroke appears to be of small magnitude and is not consistently seen across various subsets of population [10–12]. The susceptibility for ischemic stroke associated with use of oral contraceptives is higher in women who are at higher risk for ischemic stroke due to cigarette smoking, obesity, hypertension, or migraine history [10–12]. The risk of ischemic or other subtypes of stroke associated with oral contraceptive use has not been studied among patients with SCD, a population at high risk for ischemic or hemorrhagic stroke [13].

Material and Methods

The Cooperative Study of Sickle Cell Disease (CSSCD) was a multicenter, prospective study initiated in 1977 [14]. One of the objectives was to obtain data on the nature, duration, and outcome of major complications of SCD. Newborn, pediatric, adolescent, and adult patients with major sickle cell hemoglobinopathies (SS, SC, S β-thal) were eligible for enrollment in this study. A total of 4,085 women, were enrolled in Phase 1 of the CSSCD from 23 centers across the US. Information on the past history of patients was gathered by a review of the patients' autobiographical data, hospital records, and information from the patients' family members, and healthcare workers. Participants underwent a baseline examination for assessment of demographics, prior medical history, laboratory assessments, and clinical data. Post baseline data included routine follow-up examinations, measures of

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Table 1
Demographic, laboratory, and clinical characteristics of women with sickle cell disease stratified by presence or absence of oral contraceptive use.

	Women using oral contraceptives	Women not using oral contraceptives	P value
Overall no (%)	178	1079	
Age at follow-up (mean ± SD)	29 ± 5	26 ± 8	<.0001
Race			
African American	175 (98.3)	1054(97.7)	0.4
Others	2(1.1)	23(2.1)	
Co-morbid conditions			
Hypertension	8 (4.5)	26(2.4)	0.1
Diabetes mellitus	1 (0.6)	1 (0.1)	0.1
History of stroke	7(3.9)	63(5.8)	0.3
Renal insufficiency	3 (1.7)	39(3.6)	0.2
History of rheumatic fever	7(3.9)	42(3.9)	0.98
Current cigarette smoking	53 (29.8)	173(16.0)	<.0001
Alcohol use	70(39.3)	288(26.7)	<.0001
History of deep venous thrombosis	6 (3.4)	54 (5.0)	0.6
History of heart disease	17 (9.6)	139 (12.9)	0.2
G6PD deficiency	10(5.6)	57(5.3)	0.8
Treatment			
On iron replacements	6 (3.4)	39 (3.6)	0.1
On folate replacements	95 (53.4)	561 (52.0)	0.5
Exchange transfusion	23(12.9)	79(7.3)	0.01
Baseline laboratory values			
Platelets (x109/L) (95% CI)	401.2 (374.6 – 427.8)	424.9 (414.1 – 435.7)	0.1
Hemoglobin (g/dL) (mean ± SD)	9.2 ± 1.8	9.1 ± 1.6	0.5
Red blood cells (x1012/L) (mean ± SD)	3.2 ± 1.0	3.2 ± 0.8	0.6
Baseline physical examination			
Heart rate (beats/minute) (mean ± SD)	80 ± 11	84 ± 12	<.0001
Systolic blood pressure (mean ± SD)	109 ± 11	106 ± 12	0.001
Diastolic blood pressure (mean ± SD)	66 ± 10	66 ± 11	0.4
Weight (kg) (mean ± SD)	54.8 ± 9.4	45.9 ± 15.9	<.0001
Family history			
Diabetes mellitus	62 (34.8)	322 (29.8)	0.2
Hypertension	113 (63.8)	660 (61.2)	0.5
Myocardial infarction	35 (19.7)	208 (19.3)	0.9
Stroke	40 (22.5)	219 (20.3)	0.5
Follow-up events			
Ischemic stroke	3(1.7)	4(0.4)	0.03
Hemorrhagic stroke	2 (1.1)	8(0.7)	0.6
Death	13(7.3)	71(6.6)	0.7

Abbreviations used: CI, confidence interval; G-6-PD: Glucose-6-phosphate dehydrogenase; SD, standard deviation.

organ damage, and collection of acute and chronic complications. All patients in the CSSCD were followed for an additional 4-5 years according to the study protocol. Adult patients were followed every six months for regular visits. Laboratory tests, clinical evaluation, diagnostic studies, and consultations with specialists were carried out according to the specific schedule. Such evaluation was supplemented by follow-up on patients who missed visits through letters, telephone visits, and home visits as necessary to maintain adequate follow-up. Data collection for phase 1 of the CSSCD ended in 1988.

Stroke was defined as an acute neurologic syndrome caused by vascular occlusion or hemorrhage, with resultant ischemia and focal neurologic symptoms or signs lasting more than 24 hours; transient ischemic attacks (TIAs) were defined as episodes lasting less than 24 hours [15,16]. Examination of all patients by a pediatric neurologist was not required by the study, and a diagnosis of stroke was made by local investigators. Strokes were classified by the investigator at the center as hemorrhagic or infarction based on the available clinical data and imaging studies. Details of antecedent events, symptomatology, physical findings, laboratory studies, therapy, and clinical course were recorded on the appropriate data forms. The data were obtained from emergency room records, hospital charts, and/or conversation with the private physician. This ascertainment was supplemented by follow-up clinical evaluations of all patients by study team at least twice, once on admission and again four to five years later on exit from the study. Only first strokes were analyzed for this report.

We did not perform sample size calculations for this analysis since this was a secondary analysis and we used all available data for this analysis. We computed summary statistics for variables of interest with 95% confidence intervals for incidence rates. All incidence rates were expressed as the number of events per 100 patient-years of observation. We performed univariate analyses using the IBM SPSS 20 statistical software (IBM Corp. Armonk, NY). Means and frequencies were compared using one-way analysis of variance and the $[chi]^2$ method, respectively. The significant variables from univariate analysis were entered in a Cox Proportional Hazards analysis to identify the association between active oral contraceptive use at baseline interview and incident ischemic stroke. A second multivariate analysis evaluated

Table 2
Unadjusted and adjusted hazards ratios for incidence of all strokes, ischemic stroke, and hemorrhagic stroke.

Outcomes	Un-adjusted HR (95% C.I.)	P value	Adjusted* HR (95% C.I.)	P value
All stroke	3.2 (1.3-7.9)	0.01	1.9 (0.6-5.9)	0.3
Ischemic stroke	4.6(1.0-20.4)	0.04	3.6 (0.8-16.5)	0.09
Hemorrhagic stroke	1.5 (0.3-6.8)	0.6	1.2 (0.2-5.7)	0.8

Abbreviations used: CI, confidence interval; HR, hazards ratio.
* Adjusted for age, cigarette smoking status, exchange transfusions, alcohol use, body weight, systolic blood pressure, and heart rate.