Impact of Environmental Tobacco Smoke on Children With Sickle Cell Disease

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Background: Parallels between the biological effects of exposure to environmental tobacco smoke (ETS) on non-smokers and the pathophysiology of sickle cell disease (SCD) suggest that complications of SCD could be exacerbated by ETS exposure.

Objective: To determine whether children with SCD who are exposed to ETS at home have more sickle cell crises than do those who live in nonsmoking households.

Design: A retrospective cohort study in which ETS exposure was measured by using a survey of caretakers and patients.

Setting: A university-based pediatric sickle cell center.

Participants: Fifty-two of 66 eligible children aged 2 to 18 years with SCD.

Outcome Measures: The number of sickle cell vaso-occlusive crises requiring hospitalization per patient during the 2-year study (inpatient sickle cell crises). Total hospital days and hospital costs were secondary outcome measures.

Results: Patients exposed to ETS had more inpatient sickle cell crises than did unexposed patients (mean±SD, 3.7±5.7 vs 1.7±3.5; \( P = .02 \)), and this association retained significance after adjustment for important covariates (risk ratio, 1.9; 95% confidence interval, 1.3-2.7). Hospital costs were greater in the exposed group than in the unexposed group (mean±SD, $21671±$41809 vs $9705±$19146; effect estimate, 11.4; 95% confidence interval, 1.0-129.5).

Conclusions: Children with SCD who are exposed to ETS have a higher risk of sickle cell crises requiring hospitalization than do those not exposed, independent of other factors known to increase the frequency of sickle cell crises. Decreasing the exposure of these children to ETS could reduce morbidity and may provide cost savings.

such center in inland northern California designated by California Children's Services of the State of California and serves a population of approximately 2 million people (11% African American). Sickle cell disease was defined as homozygous hemoglobin S sickle cell anemia, hemoglobin S–hemoglobin C disease, or hemoglobin S–thalassemia (either β° or β' forms) and was confirmed in each patient by means of hemoglobin electrophoresis. In our clinic, patients with a history of stroke, life-threatening acute chest syndrome, or repeated severe vaso-occlusive pain crises were treated long term with red blood cell transfusions or hydroxyurea. Because these therapies are known to reduce the frequency of acute sickle cell crises, such patients were excluded from this study. In addition, patients treated at our center for fewer than 2 years were also ineligible.

Our institutional human subjects committee approved this study. Written informed consent was obtained from all caregivers, and assent was obtained from children older than 7 years.

DATA COLLECTION

The medical record of each study subject was retrospectively reviewed for hospital admissions and outpatient clinic visits, including emergency department visits, during the 2 years June 1, 1998, through May 31, 2000, immediately prior to initiation of the study. For hospital admissions, a research assistant (A.R.) blinded to patients’ exposure to ETS reviewed the dictated discharge summary to identify the most important diagnoses. Total hospital costs, based on the hospital’s estimate of the actual cost of the care provided, and length of stay for each hospital admission were obtained from the hospital accounting database. Total hospital costs did not include physician professional fees. For outpatient visits, all diagnoses documented in the physician’s clinic note were recorded. Fetal hemoglobin level was determined from the most recent hemoglobin electrophoresis performed when the patient was at least 1 year of age. A patient was considered to have a history of asthma if the condition was documented on at least 2 occasions in the medical record or if the caretaker reported that the patient was using asthma medications.

To assess interrater agreement in abstracting and recording data from the medical record, 10% of the records were randomly selected and reexamined by a single investigator (D.C.W.) blinded to whether a patient was exposed to ETS. Interrater agreement was assessed by using the κ statistic for categorical variables and the Pearson product moment correlation for continuous variables as appropriate.

Exposure to ETS was measured with a survey of the primary caretaker alone or the primary caretaker and the patient, if the patient was older than 7 years. To minimize response bias, we told participants that we were investigating “the effect of environmental factors on the severity of SCD.” A research assistant (M.H. and S.S.) blinded to the hospital admission history of the patient collected the survey data during a clinic visit or by telephone. A patient was considered exposed to ETS if they live in the home who smoked any tobacco products, either inside or outside the home, during the preceding 2 years. Exposure to ETS could not be quantified because the responding caregiver was often not the identified smoker.

OUTCOME VARIABLES

The primary outcome variable was the number of sickle cell vaso-occlusive crises requiring hospitalization per patient during the 2 years of the study (inpatient sickle cell crises). A sickle cell crisis was defined as a vaso-occlusive pain crisis (including hand-foot syndrome), acute chest syndrome, or any type of stroke. Secondary outcome variables included the total number of days in the hospital because of sickle cell crises (total hospital days), total hospital costs due to hospitalization for sickle cell crises (total hospital costs), and total number of outpatient visits for sickle cell crises that did not require hospital admission within 24 hours after the clinic visit (outpatient sickle cell crises) during the 2 years of the study. Outpatient sickle cell crises were defined as any emergency visit to the comprehensive sickle cell clinic, urgent care clinic, or emergency department. Routine well-child care and follow-up visits were excluded.

STATISTICAL ANALYSIS

For the univariate analysis, we used the Wilcoxon rank sum test to compare the 4 outcome variables of interest between patients exposed to ETS and patients not exposed. To assess the impact of potential confounding variables, we performed 2 different multivariate analyses by using generalized linear modeling for each outcome variable that appeared promising (P ≤ .10) in the univariate analysis. In the first regression model, we included only independent variables for which all patients had complete data. In the second regression model, we included variables for which some patients had missing values and excluded patients who had any such values missing. Confounding variables included age, type of SCD, and fetal hemoglobin level because these factors are known to be associated with severity of symptoms. In addition, we included history of asthma as a confounding variable because ETS is known to exacerbate asthma, which might, in turn, exacerbate SCD.

Poisson regression was used to model inpatient sickle cell crises, whereas linear regression was used to model hospital days and total hospital costs. We did not find evidence of significant overdispersion in the Poisson model. Because of the skewed distribution of hospital days and total hospital costs, we performed a logarithmic transformation of these 2 variables after adding 1 to the value of the dependent variable for each patient. Using the regression coefficients from the multivariate analyses, we estimated the total hospital costs and hospital days for each patient. For the multivariate analyses, we estimated the effect of a 1-unit increase in continuous variables or the presence of categorical variables on the number of inpatient sickle cell crises, the logarithm of total hospital days, and the logarithm of total hospital costs.

To obtain an estimate of hospital costs and total hospital days on an untransformed scale, we calculated the smeared estimate with the method of Duan. In performing this calculation, we estimated the total hospital costs and hospital days for 2 patients, 1 of whom was exposed and 1 of whom was not exposed to ETS but who otherwise had identical age, homozygous hemoglobin S sickle cell anemia, and no history of asthma.

Data analyses were performed by using statistical software (SAS version 8; SAS, Inc, Cary, NC). All tests were based on 2-tailed alternatives, and P < .05 was considered to indicate statistical significance.

RESULTS

We enrolled 52 of 66 eligible patients. The 14 eligible patients who did not enroll were older (mean ± SD, 12.6 ± 3.5 years), had a greater frequency of homozygous hemoglobin S sickle cell anemia (71.4%), and had lower fetal hemoglobin levels (mean ± SD, 4.8% ± 3.8%) than did enrolled patients. Among the eligible patients who did not enroll, 8 declined to participate, and 6 could not be contacted.

A total of 22 study subjects (42%) were exposed to ETS. Characteristics of all study patients, comparing the exposed and unexposed groups, are summarized in Table 1. On the basis of survey responses, none of the...
children or adolescents in this study smoked. Four patients had missing values for fetal hemoglobin. All patients had complete data for the remaining variables. The intrarater agreement for the medical record abstraction was strong ($\kappa = 1.0; r = 0.97-1.00$).

Patients exposed to ETS had significantly more inpatient sickle cell crises (mean±SD, 3.7±3.5 vs 1.7±3.5; $P = .02$) and total number of hospital days (23.4±31.1 vs 9.3±23.4; $P = .048$) than did unexposed patients in the univariate analysis. The differences in the number of outpatient sickle cell crises (1.4±1.0 vs 1.7±2.0; $P = .62$) and total hospital costs (mean±SD, $21 671±54 809$ vs $9705±19 146; P = .07$) between patients exposed to ETS and unexposed patients did not reach statistical significance.

### INPATIENT SICKLE CELL CRISSES

After adjustment for other covariates in the multivariate analysis, increasing patient age, homozygous hemoglobin S sickle cell anemia, and exposure to ETS were independently associated with more inpatient sickle cell crises (Table 2). The risk of sickle cell crisis was highest among patients with homozygous hemoglobin S sickle cell anemia (risk ratio, 3.1; 95% confidence interval [CI], 1.5-8.1) and those exposed to ETS (risk ratio, 1.9; 95% CI, 1.3-2.7).

Because 4 patients were missing fetal hemoglobin levels, we performed a separate multivariate analysis with the addition of fetal hemoglobin level to the regression model. In this second regression analysis, increasing fetal hemoglobin level was associated with fewer inpatient sickle cell crises (risk ratio, 0.94; 95% CI, 0.92-0.97). Exposure to ETS was independently associated with more inpatient sickle cell crises. The addition of fetal hemoglobin levels to the model changed the risk ratio and the 95% CIs by less than 0.01% for exposure to ETS.

### MEDICAL EXPENDITURES AND ETS

To assess the impact of ETS on medical expenditures for patients with SCD, we performed additional multivariate analyses to determine the association of the previously described independent variables with total hospit...
lished studies have examined the relationship between ETS and sickle cell crises, which is consistent with a protective effect. Therefore, we cannot exclude the possibility of an unmeasured confounding variable in our patient population that might be responsible for the observed associations. Furthermore, we determined ETS exposure with a caretaker and patient survey. Although this method has been shown to be a valid measure of ETS exposure, a more direct quantitative measure of ETS exposure might have allowed us to account for ETS exposure outside the home (eg, at school, work, or day care) and determine whether the association of ETS with sickle cell crises demonstrated a dose-response pattern. Such information would be helpful in providing additional evidence supporting a causal relationship between exposure to ETS and sickle cell crises in children. Finally, some of the patients in our study may have received medical care at another facility; thus, some hospital admissions may have been missed during the period of medical record review. However, this is unlikely because our center is the only one in inland northern California that treats children with SCD, and patients and caregivers were asked in the survey about hospitalizations at other institutions.

We conclude that children and adolescents with SCD who are exposed to ETS in the home, as compared with patients who are not exposed, have an increased risk of sickle cell crises requiring hospitalization. This associa-

In this study, children and adolescents with SCD who were exposed to ETS had more acute sickle cell crises that required hospitalization than did those who were not exposed. We estimated that patients exposed to ETS had 1.9 times the risk of sickle cell crisis as did unexposed patients—a substantial effect equivalent to a decrease in the fetal hemoglobin level of 11 percentage points. The effect of ETS exposure was independent of other factors, such as fetal hemoglobin level and type of SCD, known to be associated with varying morbidity and mortality among patients with SCD. Our data support the hypothesis that children and adolescents with SCD who live in smoking households have more frequent sickle cell crises requiring hospitalization than do those who live in nonsmoking households.

We also found that total hospital costs were significantly higher in the group exposed to ETS than in the unexposed group. On the basis of our calculated smeared estimate, total hospital costs were more than 10 times greater for a child who was exposed to ETS, was of average age, had homozygous hemoglobin S sickle cell anemia, and had no history of asthma than the costs for an identical child who was unexposed. However, it is important to note that there was a large variance in hospital costs, which suggests the need for a future study with a larger sample size to confirm this finding. Nevertheless, these data provide preliminary support for the hypothesis that children with SCD exposed to ETS require greater medical expenditure than do unexposed patients. Interventions designed to decrease the exposure of patients to ETS may not only decrease SCD morbidity but also provide cost savings.

To our knowledge, no authors of previously published studies have examined the relationship between SCD and exposure to ETS. However, our findings are in agreement with those of other investigators who showed that patients with homozygous hemoglobin S sickle cell anemia have more acute sickle cell crises than do patients with other forms of SCD. In addition, as other investigators have reported, we found that higher fetal hemoglobin levels were associated with reduced frequency of sickle cell crises, which is consistent with a protective effect. Our study now adds an additional, potentially avoidable, environmental exposure to the list of factors that can influence the severity of SCD.

There are several plausible biological explanations for the effect of ETS on patients with SCD. Passive exposure to tobacco smoke has been linked in a dose-dependent way with coronary heart disease in nonsmokers and chronic tissue hypoxia in adolescent children of smokers. In part, these effects are due to displacement of oxygen from hemoglobin-binding sites by carbon monoxide in ETS, which results in decreased oxygen-carrying capacity of red blood cells and tissue hypoxia. Other components of ETS are known to injure vascular endothelium, increase inflammation, and activate platelets, which results in atherosclerosis and thrombus formation. Thus, one could hypothesize that chronic tissue hypoxia, vascular endothelial cell damage, and thrombus formation from exposure to ETS could result in increased vascular occlusion by enhancing polymerization of hemoglobin S and adhesion of sickle red blood cells to damaged vascular endothelium. Alternatively, ETS could act indirectly by exacerbating asthma in patients with SCD. Unfortunately, we had an inadequate number of patients in our study to determine whether there was any modification of the effect of ETS exposure because of an interaction between ETS exposure and asthma.

Although our study results demonstrated a significant association between ETS exposure and inpatient sickle cell crises, the sample size limited our ability to detect other associations of smaller magnitude. The study was also retrospective and performed at a single institution; therefore, we cannot exclude the possibility of an unmeasured confounding variable in our patient population that might be responsible for the observed associations. Furthermore, we determined ETS exposure with a caretaker and patient survey. Although this method has been shown to be a valid measure of ETS exposure, a more direct quantitative measure of ETS exposure might have allowed us to account for ETS exposure outside the home (eg, at school, work, or day care) and determine whether the association of ETS with inpatient sickle cell crises demonstrated a dose-response pattern. Such information would be helpful in providing additional evidence supporting a causal relationship between exposure to ETS and sickle cell crises in children. Finally, some of the patients in our study may have received medical care at another facility; thus, some hospital admissions may have been missed during the period of medical record review. However, this is unlikely because our center is the only one in inland northern California that treats children with SCD, and patients and caregivers were asked in the survey about hospitalizations at other institutions.

We conclude that children and adolescents with SCD who are exposed to ETS in the home, as compared with patients who are not exposed, have an increased risk of sickle cell crises requiring hospitalization. This associa-
Parallels between the known biological effects of exposure to ETS on nonsmokers and the mechanisms of vaso-occlusive crises in children with SCD suggest that the clinical manifestations of SCD could be exacerbated by ETS exposure. With the goal of identifying new information about how to reduce morbidity and mortality in children with SCD, we sought to determine whether children and adolescents with SCD who are exposed to ETS at home have more sickle cell crises than do those who live in nonsmoking households.

We found that children and adolescents with SCD who were exposed to ETS were more likely to have an acute sickle cell crisis requiring hospitalization and greater hospital costs than were those who were not exposed, independent of other factors known to be associated with morbidity and mortality in SCD. Our study adds an additional, potentially avoidable, environmental exposure to the list of factors that can influence the severity of SCD. Decreasing the exposure of children with SCD to ETS could reduce morbidity and may provide cost savings.

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