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Daytime Pulse Oximeter Measurements Do Not Predict Incidence of Pain and Acute Chest Syndrome Episodes in Sickle Cell Anemia

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Abstract

A prospective, infant cohort study of children with sickle cell anemia was evaluated to determine the relationship between daytime pulse oximeter measurements and the incidence of pain and acute chest episodes (ACS). A total of 130 children were evaluated. The Pearson correlation between SpO_2 and pain and ACS episode rates were 0.00 (P = .97) and 0.10 (P = .27), respectively. Daytime SpO_2 cannot independently predict the subsequent rate of pain and ACS episodes.

In children with sickle cell anemia (SCA), the relationship between oxygen saturation (SpO_2) and pain and acute chest syndrome (ACS) episodes remains unclear. In practice, the measurement of oxyhemoglobin has been performed with pulse oximetry. However, because of the rightward shift in the oxygen dissociation curve in patients with sickle cell disease (SCD), the interpretation of SpO_2 can be complex and a low SpO_2 does not necessarily indicate hypoxemia.[1] Results from the Jamaican Cohort suggested no association between SpO_2 levels and sick clinic visits.[2] However, this study did not include the assessment of inpatient visits for pain or ACS episodes. Recent studies demonstrated low mean nocturnal oxygen saturation level to be associated with increased risk of subsequent painful episodes[3] and first cerebrovascular accident.[4] In a study comparing 15 children with SCA and nocturnal hypoxemia with controls, patients with sleep hypoxemia showed continued awake hypoxemia using pulse oximetry.[5] The study, however, was focused on identifying potential mechanisms of hypoxemia-induced increases in cellular markers, not on daytime hypoxemia as an independent predictor of SCD-related morbidities. In an infant cohort of children with SCA, we tested the hypothesis that baseline daytime SpO_2 reading predicts rates of pain and ACS episodes.

METHODS

Patient Population

The Cooperative Study for Sickle Cell Disease (CSSCD) study design has been reported previously.[6,7] A total of 151 African American children from the CSSCD with hemoglobin SS (HbSS) were enrolled in the study before age 6-months and had pulse oximetry data available for review. A total of 21 subjects had a missing pulse oximetry reading, and/or pain

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or ACS event. Hence, 86% (130 of 151) children were included in the study cohort for the final analysis. Subjects with HbSS were enrolled in this natural history study from 1978 through 1988. They were followed prospectively with annual follow-up and monitoring of clinical events. Pulse oximeter measurements were obtained at baseline during a routine clinic visit not associated with any acute illness. Follow-up ended in 1998. Consent and assent were obtained in accordance with the requirements and guidelines of the human subjects committees at participating clinical centers. Participation in the CSSCD was approved by the Institutional Review Board (IRB) at Washington University. Additional approval from Washington University's IRB was obtained to analyze the de-identified CSSCD data held by the National Heart, Lung, and Blood Institute.

Patient years were accrued from date of enrollment until the first of any of the following events: transfer to a non-CSSCD clinic, last required routine CSSCD visit, last special study visit, initiation of blood transfusion therapy, initiation of hydroxyurea, cerebrovascular event, bone marrow transplant or death.

Pain, ACS episodes, and cerebral infarcts were defined according to CSSCD.[6,7] Hemocrits and white blood cell count values were averaged across all annual measurements before oximetry.

Pearson correlations and linear regression, were used to test for an association between SpO_2 and co-oximetry, and between SpO_2 and pain on ACS event rates.

RESULTS

Demographics

A total of 130 participants met criteria and were included in the study. The cohort had a mean age of 9.8 years (range, 4.8 to 15.7 years) and included 65 males (50%). The mean total follow-up was 13.0 years. The mean and median follow-up after SpO_2 measurement were 3.5 years and 3.1 years, respectively. The mean PRE-SpO_2 follow-up was 9.5 years; the median was 9.2 years. The mean and median SpO_2 in the cohort were 94.1% and 95%, respectively, with a range of 75% to 100% (Figure. 1).

No Association Between SpO_2 Measurement and Pain Rate

During follow-up after SpO_2 measurement, the mean incidence rate was 1.05 pain events/patient-year (standard deviation [SD] = 1.02; 95% confidence interval [CI] = 0.96 to 1.15). The Pearson correlation between these 2 measures was 0.00 (P = .97, not significant; 95% CI = -0.17 to 0.17). Regression analysis predicting pain rate with SpO_2, controlling for known risk factors for pain (age, sex, fetal hemoglobin, and hematocrit)[7] was performed. SpO_2 had no effect on pain rate (P = .45), even after controlling for these 4 risk factors. No SpO_2 measurement was associated with an increased rate of pain.

No Association Between SpO_2 Measurement and ACS Rate

During follow-up after SpO_2 measurement, the average incidence rate was 0.20 events/patient-year (SD = 0.44; 95% CI = 0.16 to 0.24). Daytime SpO_2 did not predict subsequent ACS event rates. The Pearson correlation between the ACS incidence and resting SpO_2 was 0.10 (P = 0.27; 95% CI -0.07 to 0.27). SpO_2 measurement was not associated with the ACS rate (P = .45), even after controlling for previously identified risk factors for ACS (age, white blood cell count, hematocrit, and fetal hemoglobin).[6] No SpO_2 measurement was associated with an increased incidence rate of ACS.

No Association Between SpO_2 Measurement and Antecedent Episodes of Pain and ACS

The Pearson correlation between SpO_2 and antecedent ACS episodes was -.14 (*P* = .11; 95% CI = -0.30 to 0.03). The correlation between SpO_2 and antecedent pain episodes was .01 (P = . 91; 95% CI = -0.16 to 0.18). Thus, a single measurement of SpO_2 was not associated with antecedent episodes of pain or ACS.

DISCUSSION

Our results showed no correlation between SpO_2 and the subsequent sickle cell disease related morbidity. These findings are similar to those of Homi et al.[2] In addition, no specific daytime SpO_2 threshold was associated with higher incidence of pain or acute chest syndrome episodes.

Recurrent ACS episodes have been implicated as a cause of low baseline SpO_2. Rackoff,[8] in a study of 86 children with HbSS, determined that a history of ACS and age greater than 5 years were both associated with lower transcutaneous arterial oxygen saturation. Similar to Quinn et al,[9] we did not find the frequency of ACS episodes was associated with SpO_2 measurement.

The lack of correlation between daytime SpO_2 measurement and SCA-related morbidity does not negate the potential impact of nocturnal hypoxemia on future pain rate in SCA as previously reported.[4,5] The difference between our findings and those showing morbidity associated with nocturnal oxygen desaturation may be related to that fact that sleep, in and of itself, is a vulnerable state. Similar to otherwise healthy subjects, patients with SCD do have a fall in oxygen saturation during sleep, largely attributed to decrease in respiratory depth without change in respiratory frequency.[10] Although the Setty et al study showed that children with nocturnal hypoxemia continue to have low O_2 saturation when awake,[5] other studies demonstrated hypoxemia only at night.[11] Thus, in children with SCA, no data to date suggest that awake SpO_2 predicts SpO_2 values during sleep.

The major question raised by our negative association between SpO_2 and comorbidities is whether the outcome reflects a true negative or a false-negative association. Goodman et al. demonstrated that after completion of a study the most relevant measure is the point estimate with the 95% confidence interval and not post hoc power.[12] In this study, the 95% Pearson correlation coefficient between SpO2 and pain and ACS rates were -0.17 to 0.17; and -0.7 to 0.27, respectively. The upper boundary of each confidence interval and the narrow intervals strongly suggest that SpO_2 measurements have no relationship to future pain and ACS events. The study also has limitations inherent to the design. SpO_2 measurements were only obtained at one point in time and may not take into account the changes in SpO_2 in close proximity to an event, which may be a better correlate of SCA-related morbidity. Given the lack of correlation between SpO_2 and future pain and ACS episodes noted in our study, a longitudinal decline in SpO_2 may be more relevant than steady state SpO_2 measurements.

Daytime SpO_2 level at baseline cannot independently predict the rate of pain or ACS episodes. These findings do not negate the importance of monitoring and detecting low SpO_2 in children with SCA or assessing a change in baseline measurement. Additionally, these findings do not exclude a potential relationship between decreased baseline SpO_2 and complications other than vaso-occlusive pain and acute chest events. Future studies will be necessary to explore the possible association between daytime and nocturnal oxygen saturation levels. [1,2,11]

Glossary

ACS, Acute chest syndrome; CSSCD, Cooperative Study for Sickle Cell Disease; SCA, Sickle cell anemia; SCD, Sickle dell disease; SpO_2, Oxygen saturation.

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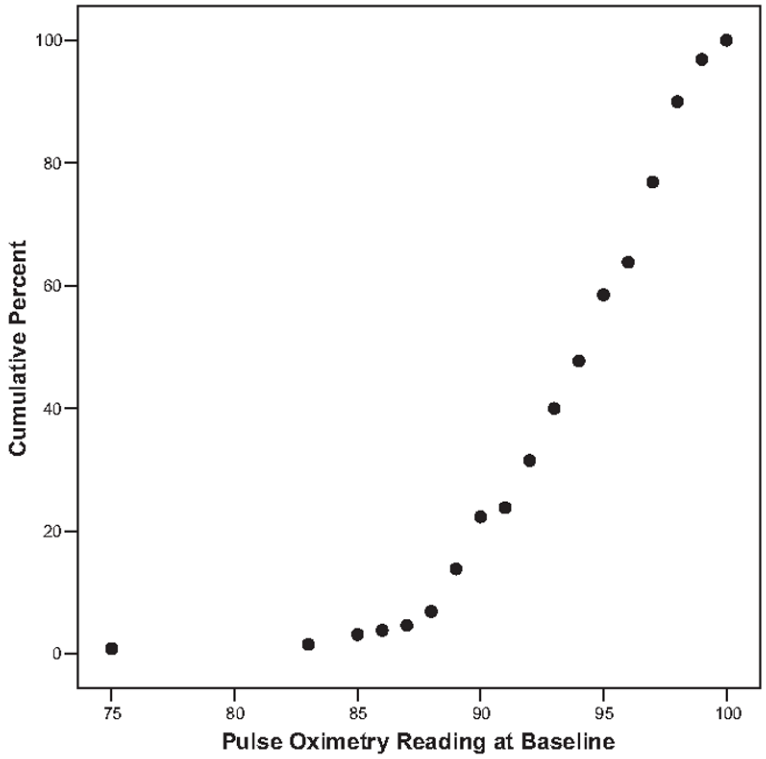

Figure.
Distribution of percent O_2 saturation by pulse oximetry in children (n = 130) with HbSS participating in the infant cohort of the Cooperative Study of Sickle Cell Disease.