Morphine Is Associated With Acute Chest Syndrome in Children Hospitalized With Sickle Cell Disease

OBJECTIVE: To determine if intravenous morphine is associated with acute chest syndrome (ACS) in children with homozygous for hemoglobin S sickle cell disease (SCD) hospitalized with acute pain.

METHODS: Health records of patients with homozygous for hemoglobin S SCD aged 2 to 18 years hospitalized with acute pain were reviewed. Patients developed ACS at least 12 hours after emergency department triage; controls did not develop ACS. Survival analyses were performed.

RESULTS: There were 38 cases and 45 randomly selected controls. The mean hourly dose of morphine 1, 2, and 3 hours before ACS and cumulative mean morphine dose up to 5 hours before ACS were significantly associated with ACS \( (P < .05) \). Adjusted analysis showed that 1 hour before ACS, the mean morphine dose was significantly higher in cases (40 µg/kg) compared with controls (34 µg/kg), and the risk of ACS increased by 23% for each additional 10 µg/kg of morphine received \( (P = .02) \).

CONCLUSIONS: We recommend close observation for ACS in hospitalized patients with SCD who are receiving morphine.

Acute chest syndrome (ACS) is a leading cause of death and hospitalization in children with sickle cell disease (SCD). It has been reported that –40% of all episodes of ACS occur in children hospitalized for acute pain due to a vaso-occlusive episode. Few studies have been published on risk factors for ACS in children with SCD. Risk factors identified in the literature specifically for ACS, such as age and genotype, are not modifiable. There is a current gap in knowledge regarding modifiable risk factors for ACS; information regarding these factors could lead to the development and evaluation of effective interventions to prevent ACS in children with SCD hospitalized with acute pain.

Systemic morphine is frequently used for pain management in children with SCD hospitalized with a painful vaso-occlusive episode. However, there is limited information in the literature about the relationship between morphine and ACS. Postulated mechanisms for an association between morphine and ACS include hypoventilation and reduced mobilization, both of which can lead to atelectasis. A recent study of treatment of painful crisis in the United States found that at the Children’s Hospital in St Louis, Missouri, the incidence of ACS in patients treated with morphine alone was 10.8%; at the Children’s Mercy Hospital in Kansas City, Missouri, the incidence was 2.1% for patients treated solely with nalbuphine, an opioid with less of a respiratory sedation effect. According to the authors, study
limitations include the differences in modes of administration of the narcotics, comparison of incidence among 2 different centers where other center-related characteristics were not measured, and lack of data on potential confounders such as pain scores. Use of morphine to optimize pain management while minimizing adverse effects may be critical to ensuring high-quality care and positive health outcomes for children hospitalized with SCD. The development of ACS in hospitalized children may be, in part, preventable with the development of guidelines on maximal morphine dosing or more vigilant monitoring of children while receiving these dosages.

The objective of the current study was to determine if morphine is a risk factor for the development of ACS in children with SCD who are hospitalized with acute pain due to a vaso-occlusive episode.

METHODS
A case-control study design was conducted by using data abstracted from hospital records.

Practice Setting and Management Guidelines
At the Hospital for Sick Children, all children with SCD and acute pain due to vaso-occlusive episodes are admitted to the pediatric medicine inpatient unit (PMIU) and are managed according to locally developed practice guidelines and computerized order sets. The PMIU is attended by general pediatric hospitalists with consultation by hematologists. Approximately 100 children with SCD are admitted to the PMIU each year.

Our recommended guidelines for children who require intravenous (IV) morphine for pain include administering an IV morphine bolus followed by continuous infusion in the emergency department (ED) at an initial infusion rate of morphine 40 μg/kg per hour. When patients were transferred from the ED to the PMIU, pediatric hospital nurses assessed and recorded level of pain by using the Oucher pain scale and monitored vital signs and oxygen saturation according to protocol. Pediatric hospitalists titrate the morphine rate according to level of pain and sedation. Patient-controlled anesthesia (PCA) should also be considered and is managed by a specialized pain team. Chest radiographs are not routinely ordered for patients with SCD and acute pain unless patients exhibit signs and symptoms of ACS or other respiratory problems.

Study Population
During the time period from January 1997 to March 2004 (inclusive), children 2 to 18 years of age were eligible for inclusion if they had a diagnosis of homozygous for hemoglobin S (HbSS) SCD and were hospitalized for acute pain due to a vaso-occlusive episode. Each hospitalization was considered a unique event and was identified by using International Classification of Diseases, Ninth Edition and Tenth Edition codes (Appendix). Hospitalizations for children who were transferred from another hospital were excluded due to difficulty in measuring drug dosages received. Hospitalizations for children on patient-controlled morphine infusions were excluded because this was a small subset of older children and youth. All hospitalizations for surgical procedures were excluded. Hospitalizations for children who were diagnosed with ACS at the time of ED visit, or within 12 hours of ED triage, were excluded from the study because we were interested in examining morphine exposure as a risk factor for ACS as a possible outcome.

Study Definitions
Cases were defined as hospitalizations for children with HbSS SCD who developed ACS during that hospital stay at least 12 hours after the ED triage. Controls were defined as hospitalizations for children with HbSS SCD who did not develop ACS during the hospital stay. ACS was defined as a new lobar or segmental infiltrate on any chest radiograph of any view performed during the hospitalization, as reported by a pediatric radiologist. This definition is consistent with the definition used by the Cooperative Study of Sickle Cell Disease and others and has been used in several publications in the literature. Two study investigators (Drs Birken and Parkin) independently reviewed all chest radiograph reports of all cases and controls. There was 92% agreement between the 2 study investigators for the diagnosis of ACS. All disagreements were settled by consensus. These study investigators were blinded to the morphine dosages received by the patients. For the purposes of the study, the time of ACS was defined as the time that the attending physician, or delegate, ordered the chest radiograph.

Data Abstraction
The following data were abstracted from the patient health record: baseline characteristics, including age, gender, and genotype; other risk factors for ACS, including history of ACS; location of pain; admission hemoglobin level; and hospital care characteristics, including length of hospital stay, ICU
admission, and blood transfusion. All morphine doses given from time of ED triage to hospital discharge or to time of ACS were abstracted directly from the detailed nursing records. Data were abstracted by 3 experienced pediatric hospital nurses (Ms Lee, Ms Pastor, and Ms Padavattan) by using a standardized data collection form.

**Statistical Analysis**

Univariate analysis with the use of $t$ tests and $\chi^2$ tests were performed to compare cases and controls. A multivariable survival analysis was performed, using morphine as a time-varying covariate. Time of ACS was censored. All variables with a $P$ value <.1 in the univariate analysis were included in the multivariate model. Results were expressed as hazard rate (HR) ratios. Sandwich estimators were used to calculate estimates of variance to adjust for repeat patient hospitalizations. Statistical analyses were conducted by using SAS version 9.1 (SAS Institute, Inc, Cary, NC).

**RESULTS**

Of the 741 hospitalizations that met inclusion criteria for our study population, 38 (5%) met the definition for cases. Forty-five hospitalizations were selected as controls by using a random computer number generator. The mean time from first morphine dose in the ED to ACS in cases was 52 hours (95% confidence interval [CI]: 43–60). Table 1 outlines the baseline characteristics of the case and control patients. There were no differences between cases and controls for pain in the location of the chest, or oxygen use in the ED, history of ACS, or pain score within the first 24 hours. Cases had a slightly lower mean ± SD hemoglobin level in the ED compared with controls (8.3 ± 1.03 vs 8.8 ± 1.6 g/dL), which was just above the threshold for statistical significance ($P = .05$).

As expected, hospital care characteristics were significantly different between cases and controls; hospitalizations for cases (compared with controls) had a longer median length of hospital stay (8.8 vs 4.9 days; $P < .0001$), increased rate of ICU admissions (19% vs 0%; $P = .003$), and increased rate of blood transfusions (50% vs 4%; $P < .0001$).

Children who developed ACS at each time point (compared with children who did not develop ACS) received significantly higher mean cumulative morphine doses during each of the time periods 0 to 1 hour, 0 to 2 hours, 0 to 3 hours, and 0 to 4 hours before the event (Fig 1). For example, 1 hour before ACS, cases received a mean of 40 ± 20 µg/kg of morphine, compared with controls, who were receiving a mean of 34 ± 18 µg/kg of morphine ($P = .02$). Likewise, children who developed ACS (compared with children who did not develop ACS) received a significantly higher mean hourly morphine dose during each of the time periods 0 to 1 hour, 1 to 2 hours, and 2 to 3 hours before the event (Fig 2). Using a multivariate survival analysis,
adjusting for ED hemoglobin and ED oxygen, the HR for mean cumulative morphine dose in the hours before ACS was statistically significant up to 5 hours before ACS (Table 2). For example, 1 hour before ACS, the risk of ACS increased by 23% for each additional 10 µg/kg of morphine received (HR: 1.23 [95% CI: 1.04–1.45], P = .02). There were no other significant differences in HR for mean cumulative morphine doses up to 24 hours before ACS (HR: 1.0 [95% CI: 0.9–1.0]). Multivariable survival analysis revealed consistent findings for mean hourly morphine doses before ACS (Table 3).

**DISCUSSION**

The results from this study demonstrate that cumulative morphine dose up to 5 hours before ACS, as well as hourly mean dose of morphine up to 3 hours before ACS, was associated with an increased risk of ACS in children with HbSS admitted to the hospital for an acute painful episode. This increase in cumulative morphine dose of 6 to 20 µg/kg in children with ACS, compared with children without ACS, is a modest but likely clinically important difference. There is some evidence in the literature to suggest that morphine may be an independent risk factor for ACS. One of the first studies reporting the use of continuous morphine infusion in hospitalized patients with painful vaso-occlusive episode reported 31% of children receiving morphine infusion developed ACS, compared with 18% of children who received other pain medication or only intermittent bolus dosages of morphine. A study using a case-crossover design showed no association between morphine dosing and ACS, although the study was underpowered.

One mechanistic explanation for why high doses of morphine increase the risk of ACS is increased sedation leading to hypoventilation. Alternative explanations for our finding of an association between morphine and ACS must be considered. Levels of pain and morphine dosages are likely highly correlated, raising the possibility that pain itself is an important variable in the causal pathway to the development of ACS. In our study, there were no differences in the proportion of children experiencing chest pain in the ED. Mean pain scores within the first 24 hours of admission between cases and controls were not significantly different for those children in whom pain scores were recorded. Due to the retrospective nature of this study, a thorough examination of pain at each time point throughout the hospital admission was not available for analysis, and this is a significant limitation of the study. This alternate explanation, however, would not account for the previously published proven reduction in risk of ACS with the use of incentive spirometry.

Strengths of the study include detailed data abstraction from hospital records for dosage of morphine at each time point by experienced pediatric hospital nurses. The use of time-varying analytical techniques allowed for changes in morphine dosage to be taken into account in the multivariable survival model. The use of survival analysis also effectively expands the "control" observations. At each event time point

**TABLE 2** Adjusted Multivariate Survival Model and HR (95% CI) Mean Cumulative Morphine Dose

<table>
<thead>
<tr>
<th>Hours Before ACS</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>1.23 (1.04–1.45)</td>
<td>.02</td>
</tr>
<tr>
<td>0–2</td>
<td>1.13 (1.01–1.25)</td>
<td>.03</td>
</tr>
<tr>
<td>0–3</td>
<td>1.09 (1.01–1.17)</td>
<td>.02</td>
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<tr>
<td>0–4</td>
<td>1.06 (1.01–1.12)</td>
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</tr>
<tr>
<td>0–5</td>
<td>1.04 (1.00–1.09)</td>
<td>.05</td>
</tr>
</tbody>
</table>

The model was adjusted for ED hemoglobin and ED oxygen levels.

**TABLE 3** Adjusted Multivariate Survival Model and HR (95% CI) Mean Hourly Morphine Dose

<table>
<thead>
<tr>
<th>Hours Before ACS</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.23 (1.04–1.45)</td>
<td>.02</td>
</tr>
<tr>
<td>2</td>
<td>1.18 (1.02–1.36)</td>
<td>.03</td>
</tr>
<tr>
<td>3</td>
<td>1.19 (1.05–1.34)</td>
<td>.001</td>
</tr>
<tr>
<td>4</td>
<td>1.10 (0.97–1.26)</td>
<td>.14</td>
</tr>
</tbody>
</table>

The model was adjusted for ED hemoglobin and ED oxygen levels.
Other limitations to this study include the retrospective case-control design. A prospective design would require a very large sample size, with multiple centers, a well-documented challenge for studies in SCD. Generalizability of these results may be limited by the use of data from 1 hospital center. The Hospital for Sick Children, however, has a large SCD program, and local practice guidelines regarding morphine use in painful crisis are readily accessible. Other potentially important factors related to ACS, including hydration, were not evaluated in this study. Of note, assessment of hydration status in children can be challenging, and the important signs may not be documented appropriately for use in a retrospective design. Additional information on medication, including nonnarcotic pain medication, was not available. Incentive spirometry has been shown in a randomized controlled trial to reduce ACS in children. We did not collect baseline data on prescription of incentive spirometry in the ED; a sensitivity analysis including prescription of incentive spirometry on the first day of admission was performed, with no impact on the results (results available on request). Patients on PCA were excluded; in our hospital, this is a small group of patients managed by a specialized pain team, rather than the hospital team, and the results are therefore only generalizable to patients not on PCA. Patient and practice characteristics should be taken into account when considering the results of this study.

There are varying diagnostic criteria for ACS used in the literature. We used the radiologic definition from the Cooperative Study of Sickle Cell Disease, which defines ACS as a new pulmonary infiltrate on chest radiograph. Since this study was performed, a report from the Comprehensive Sickle Cell Centers proposed definitions for all complication of SCD, including ACS, to support greater accuracy in SCD studies. This definition included radiologic definition plus the addition of 1 of the following clinical findings: reduced oxygen saturation or Pao₂, tachypnea, intercostal retractions, nasal flaring or accessory muscle use, chest pain, cough, wheeze, rales, and fever; it does not require a previous radiograph or physical examination. Even if this definition was available at the onset of the study, application of this definition would not be feasible due to the retrospective nature of the study design used, as clinical features may have been present in patients but not documented. Although not all cases or controls had a chest radiograph performed in the ED (in our institution, it is not routine to obtain chest radiographs on all children with SCD presenting to the ED with pain), all positive chest radiograph results were compared with previous films. The study could have been strengthened by the independent radiographic review by a pediatric radiologist.

Despite these limitations, it is unlikely that misclassification of cases and controls occurred, as evidenced by their differences in hospital care characteristics (length of stay, rates of ICU admission, and blood transfusion). A large prospective trial measuring levels of pain, sedation, and morphine use in children hospitalized with a vaso-occlusive episode using current definitions of ACS, and accounting for other concurrent treatment medications, is needed.

Practitioners should make all efforts to effectively manage patient pain by using both narcotic and nonnarcotic medications. Optimizing pain management with the use of nonnarcotic medications in addition to morphine medications, by using PCA, and allowing mobilization and deep inspiration may reduce the requirement and adverse effects of morphine.

CONCLUSIONS

This study suggests that there is an association between morphine dose, up to 5 hours before ACS, and ACS in children hospitalized with a painful episode. We recommend close observation of all hospitalized patients with SCD and pain who are receiving morphine for signs and symptoms of ACS, use of preventative measures such as incentive spirometry, nonopioid pain medications concomitant with the use of opioid medications, and frequent clinical assessment of pain control to reduce the morbidity associated with ACS. Although this study design does not provide a definitive causal association, we feel this association warrants further consideration and study.

REFERENCES


### Appendix ICD Codes Used to Identify Discharges of Interest

<table>
<thead>
<tr>
<th>Version</th>
<th>ICD Code</th>
<th>ICD Code Title</th>
<th>Records (n)</th>
</tr>
</thead>
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<tr>
<td>9</td>
<td>282.62</td>
<td>HbSS disease with crisis</td>
<td>1081</td>
</tr>
<tr>
<td>9</td>
<td>282.61</td>
<td>HbSS disease without crisis</td>
<td>44</td>
</tr>
<tr>
<td>10</td>
<td>D57.0</td>
<td>Sickle cell anemia with crisis</td>
<td>467</td>
</tr>
<tr>
<td>10</td>
<td>D57.1</td>
<td>Sickle cell anemia with crisis</td>
<td>40</td>
</tr>
</tbody>
</table>

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