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Inpatient Management of Sickle Cell Pain: a Snapshot of Current Practice

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Abstract

The Sickle Cell Disease Clinical Research Network (SCDCRN) designed the PROACTIVE Feasibility Study (ClinicalTrials.gov NCT00951808) to determine whether elevated serum levels of secretory phospholipase A2 (sPLA2) during hospitalization for pain would permit preemptive therapy of sickle cell acute chest syndrome (ACS) by blood transfusion. [1, 2] While PROACTIVE was not designed to assess pain management and terminated early due to inadequate patient accrual, collection of clinical data allowed a “snapshot” of current care by expert providers. Nearly half the patients admitted for pain were taking hydroxyurea; hydroxyurea did not affect length of stay. Providers commonly administered parenteral opioid analgesia, usually morphine or hydromorphone, to adults and children, generally by patient-controlled analgesia (PCA). Adult providers were more likely to prescribe hydromorphone and did so at substantially higher morphine equivalent doses than were given to adults receiving morphine; the latter received doses similar to children who received either medication. All subjects treated with PCA received higher daily doses of opioids than those treated by time-contingent dosing. Physicians often restricted intravenous fluids to less than a maintenance rate and underutilized incentive spirometry, which reduces ACS in patients hospitalized for pain. [3]

Keywords

Vaso-occlusion; opioid; spirometry; acute chest syndrome; PROACTIVE; fluid management; occlusion; hydroxyurea
The most common cause of hospitalization of people with sickle cell disease (SCD) is the acute pain episode. [4] ACS is defined as new clinical pulmonary findings and a new infiltrate on chest radiograph. [5] nearly 50 percent of ACS is diagnosed during hospitalization for other complications. [6] The 237 patients (169 SS, 42 SC, 15 Sβ- thalassemia, 11 Sβ+-thalassemia) enrolled in PROACTIVE from 25 centers included 118 males and 119 females. Mean age of enrolled patients was 19.3 years (range 2.0-68.0); there were 122 children and 115 adults (age >/= 18 years). One hundred-one enrolled on the day of admission and 114 the day after; 22 enrolled on day 3. Ten subjects were randomized to receive transfusion or not; the remainder were monitored in an “Observation” arm of the study. Mean duration of hospitalization was 4.1 days (range 1-11) for children and 5.0 days (range <1-40) for adults. This average length of stay for pediatric subjects is comparable to that estimated from the Healthcare Cost and Utilization Project (HCUP) Kids’ Inpatient Database (KID): 4.4 days [7] in 1997 and 4.7 days in 2000. [8]

Pain most commonly occurred in the lower extremities in both adults (66%) and children (54%). Back pain was second most prevalent (44%), especially seen in adults over age 35 (73%). Abdominal pain was most common in children age 2-9 years (25%). Seventy-seven percent of all patients complained of chest or back pain. Incentive spirometry administered at ten puffs every two hours while patients were awake was shown in 1995 to significantly reduce the risk of ACS in patients hospitalized with pain at these sites; many now use incentive spirometry on all inpatients requiring opioid analgesia. Underutilization of this safe, inexpensive intervention has been reported; [9] only 54% of our patients (60% of children and 47% of adults) and 56% of those with chest/back pain received protocol-recommended spirometry. Spirometry prescription differed between participating sites: rates ranged from 0 to 100% (median 50%). This low utilization could reflect unavailability, provider oversight or physicians’ disenchantment with patient usage of spirometry when prescribed.

On the day of enrollment, 224 (94%) patients received parenteral opioid analgesia. Of those, 132 (58.9%) received parenteral opioids only (85 by PCA), 75 (33.5%) parenteral (48 by PCA) and oral opioids, and 17 (7.6%) oral opioids only. By day 3 of study participation, 69 (30.8%) received parenteral opioids only, 43 parenteral and oral opioids, 38 (17.0%) oral opioids only, and approximately one-third received no opioids (Figure 1).

The most common parenteral opioids prescribed on day 1 were morphine (n= 80) in children and hydromorphone (n= 67) in adults. Table I (supplementary material online) depicts total daily dosages (per kilogram of body weight) by age group and mode of administration (PCA or intermittent) for those who received only parenteral therapy. Hydromorphone doses converted to morphine equivalents (one milligram of hydromorphone equivalent to 6.67 mg morphine) were two to four times morphine doses; physicians may have used hydromorphone to treat more severe pain or for patients who could not tolerate morphine side effects at required higher doses. However, in the recently published IMPROVE trial, also from the SCDRN, [10] equivalent morphine and hydromorphone doses were study-mandated on enrollment, and physicians did not administer either medication in higher morphine-equivalent total doses than the other. In PROACTIVE, adolescent patients received approximately half the dosage of adult patients, with somewhat higher morphine...
equivalents delivered to those receiving hydromorphone; a similar difference in pediatric versus adult opioid dosage was observed in the IMPROVE study, in which all participants were treated with PCA. Eighty-seven (36.7%) patients reported using opioids prior to admission (68 adults and 19 children), most commonly oxycodone (50), hydromorphone (20), morphine (19), and hydrocodone (15). The package insert for hydromorphone (Purdue Pharma L.P.) suggests it be used only in persons who are opioid tolerant; it may be that the sizable number of adult patients arriving at the hospital taking oral opioids contributed to this higher adult dosage. The nearly two-thirds of those treated with PCA received larger daily opioid doses than those not treated with PCA; perhaps patients known to be difficult to adequately treat with intermittent parenteral opioids are more likely treated with PCA and require higher doses. Alternatively, physicians relying on intermittent analgesic therapy may prescribe suboptimal analgesic therapy. Our data were inadequate to reveal the most popular dosing schedules or to illuminate efficacy or toxicity.

Hydroxyurea therapy reduces the frequency of hospitalizations for pain by approximately 50% in adults [11] but is underutilized. [12] Though hydroxyurea is not yet FDA-approved for children, some recommend off-label use [13]; completion of a trial in infants/young children (BABY HUG) indicating safety and substantial clinical benefit [14] may encourage further pediatric use. Forty-three percent of patients, 42% of children (34% of children < 10 years) and 43% of adults (59% over age 35), reported taking hydroxyurea at home prior to admission. Among those with Hb SS or Sβ0-thalassemia, 93 of 183 (51%) were taking hydroxyurea, and 6 of 42 (14%) with Hb SC. That so many admissions occurred despite hydroxyurea treatment may seem disheartening, but pain episodes tend to cluster in subgroups of patients, and those admitted for pain likely had previous admissions and were thus prime candidates for hydroxyurea therapy. [4] Dose escalation to maximal tolerated dose was required in the Multicenter Study of Hydroxyurea (MSH); [11] that we saw no difference in white cell count on enrollment (12.42 +/- 4.64 vs. 13.97 +/- 4.85 x 10^9/L, p=0.06 for those taking or not taking hydroxyurea, respectively) suggests dosing may have been less aggressive and/or compliance suboptimal in PROACTIVE patients. In a recent analysis of the MSH trial, average length of stay for adult subjects was approximately 7.7 days, reduced to 5.9 days in hydroxyurea responders; [15] in our cohort there was no significant difference between Hb SS patients who took or did not take hydroxyurea in hospital length of stay (4.49 +/- 2.63 vs. 4.69 +/- 4.97 days, respectively, p=0.74).

Seventeen percent of 200 patients enrolled in the study five years of age or older who did not have or develop ACS or other infection were nonetheless febrile on day 1 of enrollment; 49 (24.5%) had at least one fever during their hospital stay, and 100 (50%) had at least one elevated respiratory rate. Reduced oxygen saturation (O2 saturation \( \leq 95\% \)) occurred at least once in 55%, and saturation \( \leq 90\% \) occurred in 12.5% of patients, most commonly in younger children (age 5-9 years) (17.9%) and older adults (age 36+ years) (19.0%). Sixty participants (25%) received supplemental oxygen on day 1 of enrollment; of those, 19 were children. Chest radiographs were ordered for 191 (81%) participants; 135 radiographs done were study-mandated and 160 clinically indicated (62% on day of enrollment). The most commonly reported clinical indication was chest or back pain (36.2%); 42.5% of 2 to 9 year-olds had fever as the indication. Of 147 clinically indicated radiographs performed before a diagnosis of ACS, 27 (18%) showed ACS; only 10% of participants developed ACS.
Identification of risk factors for ACS including elevation of sPLA2 might allow more discriminating use of radiographs; such potentially indicative risk factors are under analysis.

Supportive care among enrolled patients varied considerably. Children with sickle cell pain crisis are somewhat dehydrated (average 4%) on admission and replacement therapy has been recommended. [16] However, because SCD care providers now recognize ACS as a common, serious complication of pain management potentially exacerbated by pulmonary edema, [17] they are cautious in use of fluids. Only 7% of participants received parenteral fluids at a rate of 1.5 times maintenance or greater (Table II) (supplementary material online). Twenty percent of children and 42% of adults received fluids at a rate less than 0.5 maintenance, and 8 were given no parenteral fluids. Only eight sites administered fluids at a maintenance rate or above to more than half their patients; seven sites provided at least half their patients with less than 0.5 maintenance fluids. Fluid preferences did not appear to be population related (children versus adults). While most patients likely take additional fluids by mouth, oral intake is often erratic and poorly quantitated. Whether the PROACTIVE investigators’ restrictive approach to fluid provision reduced the incidence of ACS and/or prolonged pain duration is uncertain.

Thirty-nine patients underwent blood transfusions during their hospitalizations for clinical indications. Thirty-one were transfused at least in part for low or worsening hemoglobin; a drop in hemoglobin concentration is commonly seen during acute pain episodes, [4] and our data support the need for careful monitoring of hemoglobin levels. Ten were transfused for ACS and/or hypoxemia; seven had both indications. Five indicated persistent pain as a contributing factor to the decision to transfuse though this is not a well-established clinical indication.

The most common specifically reported complication during enrollment was ACS (27 subjects (11.4%)). Although a fourth of patients had fever during their stay, infection (1 urinary tract infection, 1 positive blood culture for coagulase negative staphlococcus, 1 positive antigen test for influenza A and B, and one “sepsis”) was uncommon (2.1%). Notably, venous thromboembolism did not occur, though four (all adults) of the ten randomized patients received enoxaparin, presumably as thromboprophylaxis.

**Methods**

**PROACTIVE Feasibility Study Design**

Thirty-one centers were encouraged to enroll patients with Hb SS, SC, or Sβ-thalassemia age 2 years or older admitted for pain; exclusion criteria included transfusion within 60 days prior to randomization or treatment with corticosteroids, coexisting conditions, pregnancy or preferences/conditions that might require or preclude transfusion. A daily serum level of sPLA2 was obtained during the initial 72 hours of study participation; participants with elevation of sPLA2 >/= 100 ng/mL, temperature >/= 38°C and no evidence of ACS on chest radiograph within a 24-hour window were eligible for the randomized trial of pre-emptive transfusion.
Participant Monitoring

A medical history soliciting clinical events and prescribed medications currently being taken (without dosages) was performed on enrollment and recorded. Complete data regarding opioids administered were reported for all subjects; non-opioid medications were reported only on randomized subjects. Vital signs were measured every 4 hours at a minimum. The highest daily temperature, heart rate, respiratory rate, and blood pressure and the lowest oxygen saturation from enrollment to up to 72 hours or discharge were recorded. Subjects with infection were excluded from analyses of vital signs, as were children less than age 5 years due to rapid changes in normal values. Tachypnea was defined as a respiratory rate > 20 breaths per minute (> 25 breaths per minute for children age 5 – 9 years) [18] and tachycardia as a pulse rate > 100 beats per minute. Oxygenation status by either pulse oximetry or arterial blood gas on room air (after an appropriate washout period of at least ten minutes) was required and recorded at least once daily; for patients on supplemental oxygen who could not tolerate withdrawal of supplemental O₂, oxygen flow rate and FiO₂ were recorded. All adverse events, whether sickle cell-related or not, were reported and available for analysis.

Pain Management

Sites of pain were recorded on standardized forms; duration and severity were not. Guidance given local investigators regarding pain management was solely as follows:

After randomization, subjects will receive all therapy and monitoring that is considered standard of care for subjects with pain. This care will include the use of pain medications, intravenous fluids, and incentive spirometry.

All opioid analgesics with dosage and mode of administration were reported on study forms. Nonopioid medications were recorded at the discretion of local investigators and thus not useful for analysis.

Chest Radiographs

Guidelines given to local investigators for performance of chest radiographs were:

- a radiograph should be done for fever or other clinical indication as standard of care;
- for patients who met eligibility criteria for randomization (sPLA₂ ≥ 100 ng/mL, fever, and negative chest radiograph within the same 24-hour window), a repeat radiograph (to be ordered STAT) was required if the chest radiograph was not performed within the last 12 hours of the 24-hour window;
- for patients who did NOT meet randomized trial eligibility criteria, a CXR was required at 72 hours or at discharge if discharge occurred prior to 72 hours.

The indication for all radiographs was recorded.
Intravenous Fluids

Total volume of daily intravenous fluid administered was reported; fluid electrolyte content was not. For this analysis, maintenance requirements were estimated using the Holliday Segar Formula (maintenance fluids (mL/day) = 100 mL/kg/day for the first 10 kg; 50 mL/kg/day for the next 10 kg; and 20 mL/kg/day for each additional kg). [19] Actual fluids administered were compared using a proportion of the calculated maintenance rate and analyzed as ratio < 0.5; 0.5-<0.75; 0.75-<1; 1-<1.25; 1.25-<1.5; or >/= 1.5. Indications for red cell transfusion were reported.

Statistical Analysis

Statistical analyses were performed with SAS® release 9.2 (SAS Institute, Cary, NC). Descriptive statistics were reported as the number and percent, the mean and standard deviation/standard error, or the median and range. Differences in categorical variables were tested by chi-square or Fisher’s exact test and differences in continuous variables were tested by t-test.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Route of administration of opioids by day of study participation in children (a) and adults (b).