Objective: “To (1) report the total IV morphine sulfate equivalents (in milligrams) administered throughout the entire ED visit and during the first 6 inpatient hours, if the patient was admitted; (2) investigate the frequency of abnormal vital sign findings (low respiratory rate or oxygen saturation) and the need for interventions (opioid reversal or resuscitation measures) that occurred during the data collection time frame; and (3) identify key predictors of abnormal vital signs and the need for rescue interventions” (p 228)

Methods: A chart review at Northwestern University’s academic emergency department (ED) with a 4-year emergency medicine (EM) residency, 100 staff nurses, 30 ED faculty, and 40 EM residents. Adults >18 years with SCD treated in the ED between Aug 2008 and Sep 2009 were identified by ICD-9 codes. Exclusion criteria included allergy to morphine or hydromorphone, abnormal vital signs upon arrival (T > 38.3 C, heart rate > 110 beats/minute, respiratory rate <10 or >24, pulses ox <93% on room air), or the presence of specific symptoms including atypical chest pain, shortness of breath, severe headache, dizziness, mental status symptoms, priapism or abdominal pain. (p. 228)

A multidisciplinary sickle cell disease (SCD) quality improvement team (hematology + ED nurses/physicians) created the analgesic protocol depicted below guiding ED nursing to administer initial 2 mg hydromorphone (or 10 mg morphine) (+ 600 mg Ibuprofen + PRN diphenhydramine) prior to physician evaluation then second & third dose after notifying the ED physician. A minimum of 20 minutes was required between doses. A sedation score precluded administration of additional analgesia. If oxygen saturation fell below 93% on room air, the nurse discussed the situation with the physician prior to administering more opioid analgesia. (pages 228-229)

Using equianalgesic ratios of 10 mg IV/SC morphine = 1.5 mg IV/SC hydromorphone = 100 µg IV/SC fentanyl = 20 mg oral oxycodone, chart abstractors pulled total opioid dosing during the ED stay and first 6-hours of hospital stay. A random sample of 80 visits (13% of total) were re-abstracted by a second research assistant blinded to the initial assistant’s abstraction and demonstrated Pearson r = 0.84 (good interrater reliability). The lowest recorded respiratory rate and oxygen saturation were abstracted with study team consensus of <10 breaths/minute or oxygen saturation <92% deemed “abnormal”. “ED and inpatient nursing narratives were reviewed for any Rapid Response or Code Team activation, naloxone administration, vasoactive medications for hypotension management, assisted ventilation, or endotracheal intubation.” (p 230)
Potential predictors of abnormal vital signs abstracted included age, gender, race, ethnicity, and length of time in the ED. Multiple logistic regression was used to identify factors predictor of abnormal vital signs.
### Critical Review Form: Harm

<table>
<thead>
<tr>
<th>Guide</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Are the results valid?</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Did experimental and control groups being the study with a similar prognosis?</strong></td>
<td></td>
</tr>
<tr>
<td>Did the investigators demonstrate similarity in all known determinants of outcome; did they adjust for differences in the analysis?</td>
<td>No – very little patient data provided on mean age, home opioid dosing, number of prior ED visits, opioid abuse disorder, socio-economic status, health literacy, access to outpatient care, interval since last ED visit or admission, or individualized care plans.</td>
</tr>
<tr>
<td>Were exposed patients equally likely to be identified in the two groups?</td>
<td>Unknown – no demographic or opioid exposure details provided comparing the two with respiratory rate &lt;10 or the 61 patient visits with oxygen saturation &lt;92% with those visits without those adverse events.</td>
</tr>
<tr>
<td><strong>Did experimental and control groups retain a similar prognosis after the study started?</strong></td>
<td></td>
</tr>
<tr>
<td>Were the outcomes measured in the same way in the groups being compared?</td>
<td>Yes – chart review presumably performed in the same fashion for each patient. Of course, charting for each patients (upon which chart review dependent) varies from nurse to nurse and physician to physician.</td>
</tr>
<tr>
<td>Was follow-up sufficiently complete?</td>
<td>Yes – up to 6 hours for those admitted.</td>
</tr>
<tr>
<td><strong>What are the results?</strong></td>
<td></td>
</tr>
<tr>
<td>How strong is the association between exposure and outcome?</td>
<td>Weak associations noted, but in general “the larger the dose administered and the shorter the time interval, the more likely patients were to exhibit an abnormal vital sign” (p 232)</td>
</tr>
<tr>
<td>• Male patients 1.987x (95% CI 1.107-3.566) as likely to develop an abnormal vital sign</td>
<td></td>
</tr>
<tr>
<td>• Increased ED LOS (undefined) 1.359x (95% CI 1.204-1.533) as likely to develop an abnormal vital sign</td>
<td></td>
</tr>
<tr>
<td>• For every 10 mg increase in morphine sulfate equivalents IV, patients were 1.057x (95% CI 1.204-1.533) more likely to experience an abnormal vital sign</td>
<td></td>
</tr>
<tr>
<td>Nearly half of the 61 episodes of low oxygenation were 90%-91%</td>
<td></td>
</tr>
<tr>
<td>No record was found of naloxone or vasoactive medication administration, nor of resuscitative measures being required.</td>
<td></td>
</tr>
<tr>
<td>How precise is the estimate of the risk? (i.e. what 95% CIs were associated with the results?)</td>
<td>The Confidence Intervals cross unity (threshold for no difference) for age and dose-time (see 95% CI above and in Table 3, page 231)</td>
</tr>
<tr>
<td><strong>How can I apply the results to patient care?</strong></td>
<td></td>
</tr>
<tr>
<td>Were the study patients and their management similar to those in my practice?</td>
<td>Probably – academic urban ED with 4-year residency. Uncertain of socio-economic status, health literacy, or access to outpatient care.</td>
</tr>
<tr>
<td>Was the duration of the follow-up adequate?</td>
<td>Yes – 6 hours post-ED for admitted and duration of ED visit for those in ED is adequate.</td>
</tr>
<tr>
<td>What was the magnitude of the risk?</td>
<td>Very small, providing objective evidence of safety of larger doses of morphine for sickle cell patients.</td>
</tr>
<tr>
<td>Should I attempt to stop the exposure?</td>
<td>No, not based upon this evidence.</td>
</tr>
</tbody>
</table>
Limitations

1) No cited adherence to emergency medicine chart review methods (including Gilbert 1996, Worster 2004, or Kaji 2014), including training of data abstractors, blinding of data abstractors, or management of missing or incomplete data.

2) Inadequate description of patient demographics or potential confounders.

3) No adjustment for introduction of electronic medical record during study period as potential confounder.

4) Multiple potential predictors of abnormal vital signs not evaluated, including home opioid dose, interval since last home opioid dose, interval since last ED visit, and number of distinct SCD pain sites.

5) No details of logistic regression inclusion criteria or model fit provided.

6) With 72 patients and 603 visits, likely underpowered for relatively rare safety outcomes.

Bottom Line

Low quality chart review study demonstrating no adverse respiratory events associated with higher morphine-equivalent opioid doses associated with sickle cell vasocclusive pain crisis management in one urban academic ED. These results provide weak evidence of safety for sickle cell pain protocols using higher opioid doses.