Critical Review Form
Therapy

PGY-1

A randomized controlled trial comparing two vaso-occlusive episode (VOE) protocols in sickle cell disease, Am J Hematol 2018; 93: 159-168.

Objectives: **To conduct "a randomized controlled trial (RCT) in two EDs to (1) compare changes in pain scores from arrival to discharge between patients with (sickle cell) vasocclusive episode (VOE) randomized to a patient-specific or standard (weight-based) analgesic protocol and (2) explore protocol differences in secondary outcomes (pain experience, hospital utilization, side effect, and safety) between protocols." (page 159)**

Methods: **A 2-site, open-label, prospective randomized controlled trial at Northwestern University (Chicago) and Icahn School of Medicine's Mt. Sinai Hospital (New York City). Adults aged 21 years or older were randomized by research staff (during an episode of ED care or during inpatient care or during a sickle cell clinic visit) to either a patient-specific or weight-based analgesic protocol to be used during future ED visits for VOE. Exclusion criteria included sickle cell trait (not hemoglobin SS, SC, SB+, or SB-), allergic to both morphine and hydromorphone, had existing care plan stating no hospital admission for pain control, non-English speaking, >24 ED visits in prior 12 months, or presented with acute organ dysfunction that could impact opioid tolerance. (p. 160)**

Patients randomized to the patient-specific analgesic protocol received an ED opioid dose based on their current chronic opioid therapy and previously effective VOE management. This dose was quantified by their SCD provider by combining all long acting and short acting opioids taken by the patient at home during a 24-hour period converted to IV morphine equivalents. Then, 20% of patient's maximum home opioid dose converted to IV morphine or IV hydromorphone was calculated and compared to doses administered in recent ED visits. Discrepancies of >10% were reviewed by the research team before the patient-specific dose recorded with the final dose erring on low side for safety. Since NHLBI recommendations for "standard dose" are not specific, investigators used a weight-based protocol as the comparator: 0.02 mg/kg for hydromorphone or 0.1 mg/kg for morphine. Each patients' analgesic protocol was placed in the hospital's electronic medical record and "popped up" when ED providers ordered analgesics for study patients. Research assistants conducted patient interviews every 30 minutes for primary and secondary outcomes. Research assistants also conducted medical record review at 30 days to identify ED recidivism or hospital admission at 72 hours, 7- and 30-days. (p. 160)

The primary outcome was >13 mm reduction in pain per episode of ED care. Based on sample size of 126 visits (63 in each arm), a 13 mm or greater improvement in pain had 80% power to detect pain improvement with a two-sided alpha of 0.05. The Data Safety Monitoring Board halted the study because "we had enough data to conduct analysis". (p.

160) Secondary outcomes included evaluations of "pain experience", hospital utilization, and opioid analgesia safety. (p 160-161)

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Guide	Comments
Are the results valid?	
Did experimental and control groups being the study with a similar prognosis?	
Were patients randomized?	Yes. "Participants were randomized by research staff after consent, to patient-specific or weight-based protocols during future ED visits for VOE for the study duration without crossover." (p 160)
Was allocation concealed? Was it possible to subvert the randomization to ensure a patient would be "randomized" to a particular group?	No. "Allocation was 1:1 with permuted block sizes of four, stratified by site and conducted by the statistician. The study was unblinded to study staff and patients; however, patients were consented prior to randomization." (p. 160)
Were patients analyzed in the groups to which they were randomized?	Yes. "The primary analysis applying an intention-to-treat principle was conducted using a hierarchical linear mixed-effects model to test for protocol differences in change in pain from arrival to discharge…A Generalized Linear Mixed-Effect Models was used to test for protocol differences in the proportion of visits in which the patient experienced a >/= 13 mm change in pain from arrival to discharge." (p. 161)
Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Table 2 demonstrates similar age, gender, race, employment, and insurance status between patients in the two arms. Patients in the weight-based arm were more likely to have attained a secondary education (53% vs. 68%, p = 0.03) (p. 165)
Did experimental and control groups retain a similar prognosis after the study started?	
Were patients aware of group allocation?	Yes, the study was unblinded to patients. (p. 160) "After much discussion the study team felt the risks of patient refusal were too great to blind the patient to which protocol they would receive. This design was chosen because it is both pragmatic and representative of real-world clinical practice where patients are typically aware of the doses they receive." (p 167)
Were clinicians aware of group allocation?	Yes, the study was unblinded to staff. (p. 160)
Were outcome assessors aware of group allocation?	Uncertain – no clear statement of blinding outcome assessors.
Was follow-up complete?	One patient in the individualized pain plan withdrew after randomization. No additional lost to follow-up is reported. (Figure 1, p. 164)
What are the results?	
How large was the treatment effect?	• 49 patients refused participation at the beginning of the study, which may have implications for implementation of this intervention at non-academic hospitals. • 106 patients were enrolled and randomized, and 52 had a total of 126 ED visits over the 13-month study period (April 2014 thru May 2015) and the median number of ED visits/patient was 2 (and did not differ between protocols or sites). • First dose ordered ranged from 5 to 26.7 MSE for patient-specific vs. 5 to 17 MSE for standard protocol (p = 0.06) with 89% first-dose adherence for patient-specific vs. 95% adherence for standard protocol. Greater first dose variability was observed with the standard protocol, while greater delays between first and second dose noted with patient-specific protocols. • Adjusted mean pain score was 16.6 mm greater in the patient-specific group and 14.8 mm lower at time of discharge, although the % with >13 mm reduction in pain was similar between groups (84% vs. 73%, Odds ratio = 1.9 with 95% CI 0.8 to 4.5, p = 0.13)

	• Non-statistically significant reductions in time to discharge (21 minutes earlier, p = 0.14), admission rates (17.5%, p = 0.05) favored patient-specific analgesia, but higher rates of hospital readmissions at 72 hours (13% vs. 9.5%) and ED revisits at 72 hours (14.5% vs. 6.4%) noted in patient-specific analgesia. • No intubations or Narcan administration noted in either arm, but 34% less nausea/vomiting reported in patient-specific analgesic arm.
How precise was the estimate of the treatment effect? (i.e. what 95% CIs were associated with the results?)	No, the 95% CI for the primary outcome crosses unity (see above for primary outcome of % pain change >13 mm).

How can I apply the results to patient care?	
Were the study patients similar to my patient?	Yes, sickle cell patients of multiple ethnicities presenting to an academic medical center in a large city
Were all clinically important outcomes considered?	Yes, including both patient-centric outcomes (clinically significant pain relief), operational outcomes (time to disposition), and safety outcomes (desaturation, rescue medication, intubation rates).
Are the likely treatment benefits worth the potential harm and costs?	Small study with multiple threats to internal and external validity, yet "these new data provide the first compelling evidence that the benefits of individualized protocols are indeed worth the logistical investment" of establishing individualized protocols for VOE. (p 167). Whether practice-change is merited based on a single study depends on whether the individual clinician (and larger community of practitioners within a department) are early innovators, late adaptors, or laggards (per Roger's Diffusion of Innovation Theory).

Limitations

1) **With 52 patients analyzed, uncertain of reproducibility. Seemingly, significant potential for Type 1 error and no studies have yet replicated these results.**

2) **Two large academic medical centers with emergency medicine residencies, so external validity at less resourced community or non-academic hospitals uncertain. Application of PRECIS-2 may provide an objective assessment of external validity.**

3) **Lack of blinding may have introduced perception or reporting bias at the level of the patient or clinicians or outcome assessors, any or all of which could subvert randomization.**

4) **Multiple potential implementation barriers not evaluated in this study including individual clinician comfort/acceptance finding/following either protocol and the confounder of weekly efforts to curb the opioid epidemic which has grown significantly since the period of time when this study was conducted.**

Bottom Line

This two-center RCT demonstrates multiple benefits favoring patient-specific protocols for acute analgesia in sickle cell vaso-occlusive crises, including overall pain relief and reduction in opioid side effects. However, a concerning (non-significant) signal noted for increased rates of ED revisits and hospitalizations within 3-days for patient-specific

protocols. In addition, 1/3 of patients declined enrollment at the outset which may indicate patient reluctance to initially accept or adhere to patient-specific plans in real-world settings. Additional pragmatic randomized controlled trials limiting exclusion criteria and using actual non-research providers to re-assess pain/side effects would substantially enhance the external validity of these findings, if such studies reproduced the benefits and lack of harms.