Title: Comparison of Patient Centered Outcomes in the Management of Pain between Emergency Department and Dedicated Acute Care Facilities for Adults with Sickle Cell Disease

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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Sickle cell disease (SCD) is a genetic disorder of the blood that leads to severe morbidity and early mortality. It is the most common disease detected by newborn screening efforts in the United States (U.S.).[1]Between 80,000 and 100,000 individuals in the U.S. are affected by some form of SCD. The best-known burden of SCD is the vaso-occlusive crisis (VOC). These acute, excruciatingly painful events are the leading cause of hospital and emergency department utilization,[5] and can be associated with such lethal and disabling complications as acute chest syndrome and stroke.

The Emergency Department (ED) has been the standard location where patients with SCD go to seek care for the treatment of acute painful events. ED care for SCD is marked by long delays, lack of efficacy, and conflict. Nationally, forty percent of ED visits for SCD pain are concluded by hospital admissions.[7] SCD patients report not having enough involvement in decisions about their own care and also that providers do not demonstrate respect, trust, and compassion.[23] Numerous studies have demonstrated that providers hold highly negative attitudes toward SCD patients and are strongly predisposed to suspect addiction in patients presenting for VOC care.[23]

A strong body of literature supports the assertion that a subspecialty infusion center (IC), staffed by expert clinicians and delivering individualized care, can improve care quality while reducing costs. Benjamin et al. found that establishment of a dedicated SCD day hospital led to a 40% reduction in inpatient admissions relative to ED management.[24] Since this seminal finding, a number of supporting papers have confirmed that rapid assessment of VOC, close monitoring, social service support, and individualized care improves outcomes.[25-28] Yet there has never been a direct comparison between IC clinics and the ED setting

The purpose of this study is to compare outcomes between IC and ED settings in four locations around the US.

2. Objectives (include all primary and secondary objectives)

Primary outcome- time from arrival to first dose of parenteral pain medication.

Secondary outcomes:

- **a.** Outcome of acute visit – admission v discharge home
- **b.** Was patient reassessed 30 minutes after their first dose of pain medication
- **c.** Assess patient reported satisfaction and patient reported perceptions of risk (e.g. from medical errors)

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Sickle cell disease (SCD) is a genetic disorder of the blood that leads to severe morbidity and early mortality. It is the most common disease detected by newborn screening efforts in the United States (U.S.).[1]Between 80,000 and 100,000 individuals in the U.S. are affected by some form of SCD.[2] African-Americans (AA) are most affected in the U.S., as 1 per every 400 AA newborns is born with the disease. The damage SCD inflicts on sufferers is dramatic. The disease reduces life expectancy by approximately 30 years compared to the general population.[3] Furthermore, **the disease limits quality of life - as severely as does end-stage renal disease requiring hemodialysis.[4]**

The best-known burden of SCD is the vaso-occlusive crisis (VOC). These acute, excruciatingly painful events are the leading cause of hospital and emergency department utilization,[5] and can be associated with such lethal and disabling complications as acute chest syndrome and stroke. Acute and chronic pain, psychiatric co-morbidity and disease severity are factors that likely contribute to extraordinarily high levels of unemployment and decreased productivity in this patient population, with estimates that 40% of adults with SCD are unemployed.[6]

The Emergency Department (ED) has been the standard location where patients with SCD go to seek care for the treatment of acute painful events. The purpose of this proposal is to demonstrate that, from the patient perspective, the ED is not the ideal site for the management of acute, uncomplicated VOC events. While SCD is considered a rare disease in the US, the burden of ED care and subsequent hospitalization is high, and it is borne by adults. The number of ED visits by patients with SCD has increased yearly, with a 28% increase since 2006 (the first year data is available from AHRQ). Sixty eight percent of these visits are coded as acute painful crises. In 2011, there were 317,557 ED visits for people with SCD, and 82% of these visits were by people aged 18 and over. Of ED visits that resulted in hospital admissions, for every 100 people estimated to be living with the disease in the US (2006), 68.4 were for SCD, compared with 1.1 hospital admissions for asthma and 17.3 hospital admissions for CHF[7]. In addition, 30 day readmission rates for this patient population are the highest of any recorded diagnosis, at 31.9%.[8] These estimates suggest that SCD confers a significant burden on the patient, with a parallel excessive impact on the health care system.

Numerous studies show that patients and healthcare providers are dissatisfied with the quality of SCD pain management, which is currently centered in the ED.[23] ED care for SCD is marked by long delays, lack of efficacy, and conflict. Nationally, forty percent of ED visits for SCD pain are concluded by hospital admissions.[7] SCD patients report not having enough involvement in decisions about their own care and also that providers do not demonstrate respect, trust, and compassion.[23] Numerous studies have demonstrated that providers hold highly negative attitudes toward SCD patients and are strongly predisposed to suspect addiction in patients presenting for VOC care.[23]

A strong body of literature supports the assertion that a subspecialty infusion center (IC), staffed by expert clinicians and delivering individualized care, can improve care quality while reducing costs. Benjamin et al. found that establishment of a dedicated SCD day hospital led to a 40% reduction in inpatient admissions relative to ED management.[24] Since this seminal finding, a number of supporting papers have confirmed that rapid assessment of VOC, close monitoring, social service support, and individualized care improves outcomes.[25-28] Yet there has never been a direct comparison between IC clinics and the ED setting. The dearth of data has contributed to the lack of widespread adoption of this model of care. At this time there are less than 10 dedicated IC's for adults with SCD, so few patients have access to such clinics and thus acute care in the US for painful episodes continues to occur primarily in the ED. The goal of this proposal is to demonstrate that care provided in an Infusion Center is more patient centered and efficient than care provided in an Emergency Department for adults with SCD and uncomplicated VOC.

While VOC is the most common complication of SCD there are currently no evidenced based guidelines for the management of these events.[29] (RQ-1) Using an expert panel, Wang et al [30] developed a set of quality measures for the treatment of children with SCD. This group identified 41 measures that could be used to assess health systems quality of care for children with SCD. Two of these measures were for the management of acute pain. The first measure was that children who present with an acute pain episode should receive a parenteral analgesic within 60 min of registration or 30 min of triage. The second measure was that there should be a reassessment of pain level repeated within 30 min of the first dose of analgesic. There are no similar studies in adults, but the National Heart Lung and Blood Institute (NHLBI)

is finalizing guidelines, based on a systematic review of the literature, that have similar recommendations for acute pain management for all people with SCD. (RQ-1) Neither of these quality outcomes is routinely achieved in the ED setting. While there is a lack of available national data on quality measures**,** data on the average wait time to see a physician for a patient with SCD in the ED shows that it is over an hour.[31] This wait is 25% longer than for patients in the general ED population. As the physician must see the patient prior to writing an order for pain medication, it is clear that the average time to first dose of analgesia in this nationwide sample is well over an hour. Data from the Johns Hopkins ED for 2013 shows that the average time from triage to first dose of analgesia is 2 hours and 26 minutes and that the average time to reassessment after the first dose is 1 hour and 18 minutes. Similarly, in the ED at the University Hospital Case Medical Center in Cleveland the average time from triage to first dose of parenteral pain medication is 2 hours and 7 minutes. *In the Cleveland ED only 47% of the visits had any documentation of pain reassessment after medication was given* and in those where there was documentation it occurred on average 1 hour and 12 minutes after the first dose of pain medication.

There continues to be a wide variation in how acute painful events are diagnosed and managed in the acute setting because management of VOC has never been studied in a systematic fashion (RQ-1). There are no objective clinical or laboratory measures of the presence or severity of a crisis, and so the only way to confirm that a patient is having a crisis is to ask the patient (i.e., patient self-report). The current pain scales used for self-report have not been validated in this patient population.[29] It is therefore not surprising that due to this uncertainty many patients receive suboptimal care in the acute setting, especially when managed by clinicians, as in the ED, who are unfamiliar with them and who are not trained to specifically manage their disease and its complications.

The purpose of this study is to compare patient centered outcomes for those patients being treated for an uncomplicated VOC in ICs and EDs. We have designed this study based on preliminary, single site retrospective data on ICs from our participating sites which have shown similar outcomes to that of Benjamin[24]. The Johns Hopkins Sickle Cell Infusion Center (SCIC) which opened in 2008 provides acute care solely for adults with SCD. In 2008, 50% of all ED visits for VOC resulted in hospital admission at Johns Hopkins Hospital (JHH). The SCIC initially was opened 5 days a week and in 2011 increased hours to include the weekends. The SCIC has 5 treatment slots for acute care visits, and is staffed by a clinic coordinator, nurse, clinical nurse associate, social worker and physician extender. Supervision is provided by Dr. Lanzkron, who is the medical director and the proposed PI for this study. From the period February 2008 through December 2011 there were 3874 visits to the SCIC by 361 unique patients. On average, there were 3.8 visits to the infusion clinic daily (range 0-10). The average number of visits by each individual was 10 (range 1-84) or 2.5/yr. Eighty five percent of visits ended with the patient being discharged home. The remainder were either directly admitted to the hospital or sent to the ED for further treatment. *The average time to receipt of first dose of opioid from arrival to the clinic was 57.7 minutes* (95% CI 56.5, 58.8). The average time that patients spent in the SCIC was 4 hours and 55 minutes. The average pain level on arrival using the numerical rating scale (NRS), which measures pain on a scale of 0-10, was 8.4 (95% CI 8.3, 8.4). The average decrease in pain score from arrival to discharge was 2.62 points on the NRS (95% CI 2.55, 2.69). Those who went home had a significantly greater decrease in pain than those that remained for hospital care (Δ-2.9 vs. Δ-1.2, $p<0.001$). There was borderline statistical but no clinically significant difference in time to first dose of opioid for patients who were discharged home compared to those that required additional hospital care (57.2 min v 60.3 min, $p=0.06$). In examining the association of changes in pain scores with discharge disposition, we found that, after adjusting for gender, patients were 2 times (OR 2.01, 95% CI 1.85, 2.19) more likely to be discharged home for every 1 point decrease in their pain. In comparing these outcomes to the JHH ED between 4/2010-7/2012, there were 1554 total ED visits for SCD pain made by 254 unique patients. *In the ED, the average time from triage to first dose of pain medication during this time period was 190 minutes* (SD 129.8). In a model controlling for acuity in the ED, for every 10 minute increase in time to first dose of pain medication, the relative risk of admission increased by 0.7% (95% CI 1.00 1.01, $p=0.024$). Since the opening of the SCIC there has been a 22% reduction in admissions and reduction in 30 day readmissions from 39% to 22%.

A similar clinic to the SCIC opened at Froedtert Hospital in Milwaukee (FASCC) in 2011. The FASCC clinic is open weekdays and serves the needs of 300 adults with SCD. The average length of stay in the clinic is 3 hours and 96.5% of visits end with the patient being discharged home. Since this clinic opened there has been a 38% decrease in admissions and a decrease in 30 day readmissions from 61 to 28%.

Without a direct comparison of ED to IC, many argue that there is something different about the patients that receive care in an ED versus those that seek care in an IC. Further, the recent expansion in ICs has been driven primarily by economic consideration (length of stay, readmissions), rather than by patient-centered outcomes, on which there is a lack of data. Demonstrating attainment of important clinical outcomes in ICs may increase their stability and viability. **With this proposal we will demonstrate that the improved outcomes seen in an IC v. the ED are not due to differences in the type of patients seen for care but rather in the processes of care for VOC in these two sites.**

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

We will prospectively enroll patients that are seen in participating centers into a study cohort. We will then capture data from their acute visits. We will enroll participants from 4 sites: Baltimore, Cleveland, Milwaukee and Baton Rouge. When any participant is treated in either an ED or IC, data on clinical outcomes and patient experiences of care will be collected.

Baseline data collection will include: SCD genotypes and co-morbidities[35]

a. AVN
b. Gall bladder disease
c. Sickle chronic lung disease
d. Leg ulcer
e. Priapism (male)
f. Renal failure
g. Retinopathy
h. Stroke

2. Self-reported number of acute care visits and hospitalizations in the prior 12 months
3. Daily chronic pain using the Numeric Rating scale (NRS).
4. Prior and current treatments, including:
    a. hydroxyurea use
    b. chronic transfusions
    c. pain medications, (specific regimens used to treat chronic daily or intermittent pain)

After participants have consented they will be asked to contact by phone or email the research assistants about all acute care visits. In addition, the research assistant will review the daily census for IC's and ED's at the local site to identify participants with an acute care visit. Furthermore, each participant will be contacted by phone monthly and asked about acute care visits.

Once an acute care visit for an uncomplicated VOC has occurred, the following data will be collected: Time crisis started, Arrival time, Triage time, Pain level on arrival, Time to first dose of opioid, Time from first dose to nurse reassessment of pain, Time in the ED/IC, Pain level at discharge from ED/IC, Change in pain scale from arrival to discharge, Disposition at time of discharge from ED/IC (home, admit, etc.). In order to assess patient experiences of care in the acute setting, participants will be surveyed either toward the end of their acute visit or by phone within 72 hours of their visit. As reinforcement, at each monthly call, we will verify contact information and encourage participants to call us within 3 days of any acute visit. The survey tools that will be used include the Painful Crises Experiences of Care for SCD tool (PEPS); a survey of safety and a survey of patient satisfaction with ED pain management.

b. Study duration and number of study visits required of research participants. Participants will be part of the study for 18 months. During which time there will be no in person study visits. There will be monthly phone calls and contact at the time of acute care visits.
c. Blinding, including justification for blinding or not blinding the trial, if applicable. NA
d. Justification of why participants will not receive routine care or will have current therapy stopped. NA
e. Justification for inclusion of a placebo or non-treatment group. NA
f. Definition of treatment failure or participant removal criteria. NA
g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely. NA

All data collection will be done using RedCap. RedCap is a secure web based database tool that has multisite functionality. Each external site will enter their data into a single database. Each external site will only have access to their own data through the site. As the central coordinating site, Hopkins will have access to all of the data. When data collection is complete and records are finalized the data will undergo data lock. As all data will be entered into a common database merging of data will be done after data is exported from RedCap into Stata for further analysis. Merging of data will need to be done for combining the demographic data with data collected from each acute visit.

5. Inclusion/Exclusion Criteria

All individuals with confirmed SCD who live within 60 miles of the study center or who already receive regular care at the participating centers will be eligible for enrollment. The only exclusions will be patients who are pregnant, who have been stable on chronic transfusion therapy and have not had a painful episode within two years of enrollment (transfusions may prevent all acute painful events) and patients who are unwilling or unable to sign consent.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used. NA
b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed. NA
c. Justification and safety information if non-FDA approved drugs without an IND will be administered. NA

7. Study Statistics

Primary and secondary outcome variables: This is an observational study from which we will draw inferences about outcomes of care attributable to the treatment setting. As we are not randomizing patients to ED care or to IC care, we must control for confounders in the relationship between site of care and outcomes. We note, however, that there may be regional differences that impact on outcomes: percentage of high utilizers in the region, duration IC has been functioning, and ED crowding. In our study, we have clustering of individual patients by regions (n=4). We will account for both known and unknown confounders at the level of the regions.

Given the anticipated differences in patients who seek care in these settings, we propose using propensity score techniques to balance patient characteristics in the two treatment groups both within and across sites. We will use relatively new methods developed for use of propensity scores in the context of multilevel data.[42] We look towards using propensity scores for achieving balance in the distributions of covariates to allow for a causal comparison. Our treatment assignment is at the individual level and we propose using appropriate propensity weighting methods to generate valid causal inferences, under the assumption of absence of unmeasured confounders.

For causal comparisons, we adopt the potential outcome framework for causal inference.[43] Under the standard stable unit treatment value assumption (SUTVA)[44], which states that the outcomes for each patient are unaffected by the treatment assignments of the other patients, each patient has two potential outcomes corresponding to the two treatments (ED or IC care), only one of which is observed for each patient. We believe the SUTVA assumption to be true in our setting. We aim to estimate the population average treatment effect, although we may also look at the *population average treatment effect on the treated (ATT),* which we expect will be very similar.

Notation Let k = 1, 2, …, K denote number of regions and i=1, 2, …, n_k denote the number of participants in region k. Total sample size is n = $\sum_{k=1}^{K} n_k$. Each subject belongs to one of two groups, ED (control) or IC (treatment) care. Let Z_{ki} be the binary variable indicating whether the subject is in the treatment (Z=1) or control (Z=0) group. Also, let U_{ki} be a vector of subject-level covariates and V_k be a vector of region-level covariates, and $X_{ki} = (U_{ki}, V_k)$. For each subject, an outcome Y_{ki} is observed, which, in our study, can be continuous or binary. The propensity score is defined as $e(X_{ki}) = Pr(Z_{ki}=1 \mid X_{ki})$.

Fitting a Propensity Model Given the multi-region (clustered) data, we cannot use standard techniques for propensity score modeling but instead will use a *random effects model* that accounts for clustering. We have chosen this model because we are uncertain about all of the cluster-level covariates that might impact on treatment effect. The few that we hypothesize to be regional-level confounders, as described above, we will include in the model. The individual level covariates will include: SCD complications, self-reported number of acute care visits and hospitalizations in the prior 12 months, pain rating upon first arrival for care, distance from residence to site of care, and demographic variables. The random effects model to generate the propensity score is as follows:

$$\text{logit}\,(e_{ki}) = \delta_k + X_{ki}\,\beta \qquad (1)$$

This model includes individual level covariates, as well as cluster-specific intercepts due to measured and unmeasured cluster-level covariates, and a prior distribution for cluster-level main effects, $\delta_k \sim N(0, \sigma_\delta^2)$. We expect that since we will have many patients within each region (cluster), we should not have any difficulty in fitting the random-effects model. The goodness of fit of this model will be checked by conventional diagnostics of covariate balance between the ED and IC treated patients, checking the overall and within-region balance of the weighted distribution of covariates in the two groups.

Estimating an Overall Treatment Effect We will then use the inverse of the propensity score, e_{ki}, generated from the random effects model described above, to *weight the outcomes* for each individual. This will allow us to draw valid inferences about the differences between groups. We propose using a non-parametric clustered-estimator as our inverse-probability-weighted estimator.

$$\hat{\pi} = \frac{\sum_{k=1}^{K} \hat{\pi}_k w_k}{\sum_k w_k} \qquad (2)$$

Where $w_k = \sum_{i \in k} w_{ki}$, $w_{ki} = Z_{ki}/e_{ki} + (1-Z_{ki})/(1-e_{ki})$, and $\hat{\pi}_k$ is the inverse-propensity weighted treatment effect for the k-th region. This estimator accounts for clustering of the patients by region. The standard error of the estimate will be generated by bootstrapping.

To test the first hypothesis (time to pain medication), we will use the observed time to first dose (a continuous outcome) in the two groups. We do not need to use time-to-event models since there will be no censoring. We will evaluate whether the time needs to be log-transformed in order to be approximately normally distributed. To test the second hypothesis, we will describe the proportion of patients in each group that is reassessed in the first 30 minutes after dosing. We will describe the proportion of patients admitted in each of the treatment groups, using the estimator described above. For evaluations of the difference in *patient experience* of care in these two settings this likely reflects the adequacy of symptom relief during the visit and the patient-centeredness of the visit including being treated respectfully and feeling unthreatened in the environment. The outcome of interest is an ordinal measure on a scale of 18 points that we will analyze as a continuous outcome, using the estimator above. The other surveys will be analyzed similarly.

Sensitivity analysis In our sensitivity analyses, we will stratify patients into quintiles based on their propensity scores and test for differences in the outcomes of interest between ED and IC treated patients in each quintile. These quintile-specific estimates will be reported, as well as pooled estimates from application of random effects methods.

We will also estimate propensity scores using a fixed effect model rather than a random effects model (Eq 2). We might also explore the use of a doubly robust estimator, where we would model the potential outcomes using a random effects model. The results are expected to be similar.

We will also test whether our inferences are sensitive to hidden biases from unmeasured confounders. We will estimate how strong an unmeasured confounder needs to be related to both exposure and outcome to affect the inference about difference in effect in the treatment sites. Potential unmeasured confounders might be patient-preference for site of care, or local culture or climate regarding care of patients with SCD.

a. Statistical plan including sample size justification and interim data analysis.

We have based the needed sample size on the outcome requiring the most participants, the admission rate from the ED v. IC. We hypothesize that we will observe an ED admission rate of 50%[9], and an IC admission rate of 27% (an absolute reduction of at least 23%). We took the following design considerations into account in estimating the sample sizes needed to detect this difference: We have a 2-arm study (IC vs. ED) with 4 clusters (sites) per arm. With a type I error of 0.05, a type II error of 0.20 (power 0.80), and an estimated intracluster correlation coefficient (ICC) of 0.02, we will require an average of 41 participants in each cluster (site) per arm. 410 participants total (205 per arm) are required to detect our hypothesized difference in admission rate. We estimate we will observe a lost-to-follow-up rate of 18% so our total required sample size is [410/(1-0.18)] = 500 participants.

b. Early stopping rules. NA

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

The risks from this study are minimal. The participants may become tired or bored while filling out the surveys. There is also the risk of loss of privacy. Participants can choose to not participate in this study as it is not a treatment protocol there are no alternatives.

b. Steps taken to minimize the risks. All primary data to be collected will be de-identified using a unique identifier and will be kept in a secure office in a password protected computer. The data put in REDCap will be de-identified. As REDCap is a secure website and only deidentified data will be put in it the risk of loss of privacy is minimal. Every attempt will be made to assure that all locally collected data is kept in a secure environment and that all identifiers will be removed from primary data. The spreadsheet with the identifying info linked to the unique identifier will be destroyed when the REDCap database is finalized and locked.

c. Plan for reporting unanticipated problems or study deviations. Any breach of patient confidentiality will be reported to the IRB.

d. Legal risks such as the risks that would be associated with breach of confidentiality.NA
e. Financial risks to the participants. NA

9. Benefits

a. Description of the probable benefits for the participant and for society.

There will be no direct benefit to the subjects for participating in this study. What is learned from this study may improve the way in which adults with VOC are treated in the future.

Importance of the Knowledge to be Gained The knowledge gained from this first time comparison of the treatment of acute pain in SCD comparing ED's and IC's will result in a better understanding of where this treatment should occur. The study will demonstrate how IC's can provide more rapid and appropriate care for this patient population and this should lead to greater access to these services for patients throughout the US who suffer from SCD.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

We will compensate participants for time and inconvenience associated with study participation. Participants will receive $25 for completing the initial study survey, and $25 every 6 months thereafter (for a total of 18 months of follow-up), for maintaining ongoing participation and communication with the study.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.
NA