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Impact of PCA Strategies on Pain Intensity and Functional Assessment Measures in Adults with Sickle Cell Disease during Hospitalized Vaso-Occlusive Episodes


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Abstract

Clinical trials of sickle cell disease (SCD) pain treatment usually observe only small decrements in pain intensity during the course of hospitalization. Sub-optimal analgesic management and inadequate pain assessment methods are possible explanations for these findings. In a search for better methods for assessing inpatient SCD pain in adults, we examined several pain intensity and interference measures in both arms of a randomized controlled trial comparing two different opioid PCA therapies. Based upon longitudinal analysis of pain episodes, we found that scores from daily average Visual Analogue Scales (VAS) and several other measures, especially the Brief Pain Inventory (BPI), were sensitive to change in daily improvements in pain intensity associated with resolution of vaso-occlusive pain. In this preliminary trial, the low demand, high basal infusion (LDHI) strategy demonstrated faster, larger improvements in various measures of pain than the high demand, low basal infusion (HDLI) strategy for opioid PCA dosing, however,

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Disclosures

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verification in larger studies is required. The measures and statistical approaches used in this analysis may facilitate design, reduce sample size, and improve analyses of treatment response in future SCD clinical trials of vaso-occlusive episodes.

**Keywords**
sickle cell disease; pain; longitudinal models

The response to analgesic medications during hospitalized vaso-occlusive painful episode is most frequently assessed by age-appropriate measures of pain intensity. [1, 2] Use of pain interference scales has been limited by their lack of validation in this setting. Most published cohorts and small clinical trials of sickle cell pain treatment usually observed only relatively small decrements in pain intensity, suggesting limitations in assessment methods, treatment, or analyses.[3, 4] Traditional analysis techniques used in these studies often compare pain intensity at different time points, which may not optimally detect differences given the high correlation and non-independence of serial measures within the same patient. Also, studies often report only summary measures of daily pain intensity, which may obscure important within-day variability in pain intensity and response. Further, analysis of measures from only currently hospitalized patients are subject to a variant of survivor bias, such that values in later time points are only measured in patients still hospitalized, who, by definition, likely have not improved compared to discharged patients.

In a quest to find better pain assessment methods for inpatient SCD pain studies, we compared a well validated VAS (Visual Analogue Scale) score [5, 6] to several pain and functional assessment measures to in adult participants of a clinical trial comparing two different opioid PCA dosing strategies during hospitalized pain episodes. Whereas the primary outcome of a time-to-threshold analysis of the VAS score required a large sample size for adequate power, the improved efficiency of longitudinal analysis of these secondary outcomes suggested this methodology may be a more powerful paradigm for future studies of SCD vaso-occlusive episode pain.

From January 1, 2010 to June 8, 2010, a total of 1116 patients age ≥10 years were hospitalized for pain at the 31 study sites; 224 were ineligible, 915 were missed for logistic/staffing issues at sites [7], and 38 subjects (24 adults and 14 children) completed randomization and study procedures prior to trial closure. Two adult subjects and two children were withdrawn (2 inadvertent withdrawals, 1 ineligible, one withdrawal of parental permission). The mean age of adult subjects was 30.0 ± 11.0 years (range 18–52 years), and similar in both treatment arms (HDLI, 32.2 ± 11.3 years, LDHI, 27.4 ± 10.6 years). Subjects were largely African-American, with a 55% female gender distribution. The SS hemoglobinopathy phenotype, present in 81.8% of subjects, reflected the expected prevalence of more severe phenotypes in this hospitalized sample. Further characteristics of the enrolled population, trial design, assessment measures, PCA protocol, and statistical analysis plan are available in the online supplemental materials and reference [8]). Subjects randomized to the High Demand/Low infusion (HDLI) PCA treatment stayed longer than those assigned to Low Demand/High Infusion (LDHI) (Mean: 7.1 versus 3.9 days, Table 1, supplemental materials).

The daily average VAS scores were most similar in magnitude to the least pain intensity scores from the BPI and showed similar trends over time (Figure 1). The VAS models (see online supplemental materials) demonstrated a significant difference between treatments in rate of improvement but not a significant difference in average score on day 3 in this small data set (p=0.06, Table 1). Additional models (not shown) demonstrated that the estimated
treatment differences were not influenced by the inclusion of an additional covariate for baseline VAS assessment (p=0.33), by showing only a slight modification of effect size for the interaction term (~0.85 in the baseline adjusted model versus ~0.87 in the model shown in Table 1). Modeling the data based upon time of individual VAS assessments (three times daily) rather than as a daily average resulted in a slightly larger estimate of difference between treatments in rate of change (~0.97 in the adjusted model), and a slightly higher intra-class coefficient (ICC) (0.43 in the adjusted model versus 0.41 in the model shown in Table 1).

The magnitude of the pain intensity scores from the Brief Pain Inventory (BPI) varied as expected from previous experience in the day hospital setting [9]. First, among concurrent scale measures, average score on day 3 for reports of worst pain was higher than average pain, which was higher than least pain (Table 1). Second, the means for all BPI pain intensity scores decreased over time (Figure 1), and the medication relief score improved over time, reflecting the resolution of acute pain typical for this disorder. Third, the summary pain interference score and its affective and activity subscale scores showed improvement over time concurrent with the reduction in pain intensity (Figure 1). The BPI ratings of worst pain and average pain showed the largest difference between treatments in rate of pain improvement across the five day observation period (Table 1, Estimate = −1.23, −1.17, p < 0.01, Figure 1) and all BPI items showed statistically significant advantages of the LDHI treatment in rate of improvement (p ≤ 0.03, Table 1). The difference between treatments on day 3 was statistically significant only for worst pain (p=0.03, Table 1). The current pain measure was the most reliable among the BPI pain measures (ICC=0.43, Table 1), yet all BPI pain intensity measures had larger within-subject than between-subject standard deviations, reflecting substantial variability in daily pain improvement (ICC<0.5, Table 1).

Pain intensity scores from the Memorial Pain Assessment Card (MPAC) [10, 11] were very similar in magnitude to the similarly worded current pain item of the BPI, but with somewhat lower estimates of between- and within-subject standard deviation, likely reflecting its use of a continuous rather than categorical scale (Table 1). The MPAC pain intensity scores showed statistically significant differences between treatments in both the rate of improvement (p<0.01) as well as the difference in pain on day 3 (p=0.01) (Figure 1, Table 1). The MPAC mood and pain relief scores showed significant differences between treatments in rate of improvement but not differences between treatments in average score on day 3 (Table 1) and tended to improve over time consistent with reductions in pain intensity (Figure 1). The MPAC pain score appeared to be more reliable than either the VAS daily average or the four BPI pain items (ICC=0.50, Table 1).

Physical summary scores from the SF-8 were very low compared to US population means [12], with average scores in the upper 20s to lower 30s on most study days (Figure 1), reflecting the significant impact of pain on physical activities. Mental summary scores were less impacted, only being about 10 points (1SD) below US population means. Neither the SF-8 physical summary score nor the mental summary score changed appreciably over time or showed significant trends in improvement or difference between treatment arms (Figure 1, Table 1). The physical summary score appeared to be more reliable in this population than the mental summary score (ICC=0.71 versus ICC=0.50, Table 1).

The average daytime standard of care (SOC) clinical pain assessments were similar in magnitude to those of the daily average VAS, but missing data for some days for some patients made direct comparisons difficult (n=69 versus n=87, Table 1). Despite having fewer recorded measurements, the average daytime SOC scores appeared to be more reliable than the VAS (ICC=0.62 versus ICC=0.41, Table 2), likely reflecting the more frequent
daily assessments made for the SOC scores than the three VAS scores. Average nighttime SOC scores were similar in magnitude to average daytime SOC scores (Table 1). Only the average daytime SOC assessments showed a statistically significant difference between treatments in rate of improvement (p<0.01) (Table 1).

Assessment data from this initial participant cohort suggests several pain measures may be useful in this setting, which a larger study could confirm and expand. The MPAC current pain and the BPI worse pain scores were both able to identify an increase in rate of improvement for the LDHI group that was established by day 3. Given their use in other analgesic clinical trials [13], they may be more appropriate analgesic study endpoint assessments than our initial choice of daily average VAS, which had little advantage over analysis of individual serial VAS measures. Our results also suggests that the summary BPI pain interference scale is a sensitive assessment tool in this setting, as the activity and affect components of this scale showed an increase in rate of improvement for the LDHI group.

The results for these analyses were obtained by fitting longitudinal models to each of the secondary outcome scores [14, 15] (further details in online supplemental materials). These models estimated the daily rates of improvement for each treatment group while accounting for within-subject versus between-subject variability. Although the longitudinal analysis was originally planned in the protocol, the required sample size for the trial was determined by a much less-powerful primary analysis of the time to achieve a threshold drop from baseline VAS. Future studies could dramatically reduce the required number of subjects for adequate power to detect a treatment effect by planning a longitudinal analysis of the primary outcome [16]. A further improvement in power might also be obtained by analyzing the responses from different instruments simultaneously in a multiple outcomes model [17, 18]. Extensions to longitudinal rate of change models are an area of statistical research and may provide additional analysis options in the future.

There are a number of limitations to this study. The pain intensity improvement threshold set for the originally-planned time to event analysis (2.5 cm) was too small. It was achieved so quickly (in both treatment groups) that it was difficult to discern a significant difference between treatments. Although the advantage of the LDHI treatment appeared to be quite pronounced in the longitudinal analyses, it is possible that a small subset of subjects with large effect size influenced these results [19]. A larger study with a more diverse participant population will be needed to confirm these assessment and PCA treatment findings.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

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**References**


Appendix

In addition to the authors of this manuscript, the following individuals were instrumental in the planning, conduct and/or care of patients enrolled in this study at each of the participating institutions as follows:

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Figure 1.
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<td>Research Support: Glycomimetics, NIH; Consultant: Eli Lilly</td>
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Longitudinal Models

Longitudinal models were fit separately to each score response and included fixed effects for intercept, trend across study day, treatment effect (LDHI vs. HDLI), and interaction between treatment and study day and random effects for intercept, and slope across day for each subject. The models were coded so that the treatment effect reflects the difference between treatments on study day 3. The SD components correspond to the between-subject variation (among the random intercepts and slopes) and the within-subject variation (among the residuals). The intra-class correlation (ICC) represents the proportion of total variation that is between subjects. The p-value for the fixed effects intercept was <0.01 for all scores, but has no clinical relevance.

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