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SUPPORTING INFORMATION

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Impact of intranasal fentanyl in nurse initiated protocols for sickle cell vaso-occlusive pain episodes in a pediatric emergency department

To the Editor:

Although pain is a universal feature of sickle cell disease (SCD), there is limited evidence to guide management for vasoocclusive pain episodes (VOE). In 2014, the National Heart, Lung, and Blood Institutes (NHLBI) published new guidelines recommending rapid evaluation and treatment of VOE in the acute care setting, with timely pain assessments and repeat analgesia as needed to control pain. Despite these guidelines, delays in administration of parenteral analgesia are common in pediatric emergency departments (ED).[1]

Fentanyl is a potent, synthetic narcotic analgesic with a rapid onset and short duration of action. It is a strong agonist at the μ-opioid receptors, approximately 100 times more potent than morphine. Intranasal fentanyl (INF) has an onset of action of about 5–10 minutes, peaking within 30 minutes. INF 1.4 mcg/kg equates to intravenous (IV) fentanyl 1 mcg/kg (approx. 70% bioavailability),[2–6] and can provide rapid and powerful analgesia in the ED without the need for IV access. Current evidence suggests that INF is a safe and effective method of pain management for children in a variety of clinical settings, and is commonly used in the ED to control acute pain.[2] A quality improvement (QI) initiative by Kavanagh and colleagues was the first to use INF in the management of VOE in children with SCD and demonstrated improvements in time-to-first-parenteral-opioid dose, together with improved time-to-second-opioid and time-to-ED disposition. Of interest, ED discharge rates also increased from 32% to 48%, without an increase in 24-hour readmission or adverse outcomes like respiratory depression.[3] A recently published randomized placebo-controlled controlled trial involving 49 children with SCD presenting to an ED with moderate-severe pain randomized to INF (2 μg/kg, maximum 100 μg) had a greater decrease in median pain score at 20 minutes compared to normal saline placebo. We therefore evaluated the addition of INF to a nurse-initiated protocol at the Egleston Pediatric ED at Children's Healthcare of Atlanta (CHOA) for the management of SCD/VOE on time-to-first-parenteral-opioid dose administration, ED length of stay (LOS), and admission rates compared to: (1) historical control data prior to implementation of the INF protocol and (2) those who were not treated with INF during the study period. (See Supplement Methods Section for details on setting, participants, the CHOA nurse-initiated SCD-pain protocol [Supporting Information Figure 1], education initiatives utilized to ensure team buy-in, data collection, statistical analysis, and limitations.) All children with an established diagnosis of SCD (all genotypes) between the ages of 2–18 years presenting to the ED with VOE treated with intravenous (IV) opioids were eligible. Electronic medical record data were collected for a 6-month period before and after implementation of INF use to the nurse-initiated protocol. Patient/family and nursing satisfaction with INF was obtained through a Likert Scale Survey.

A total of 248 SCD visits for moderate-to-severe VOE occurred during the 6-month pilot period. Of those, 228 patients received parenteral opioids (92%), of whom 180 (79%) received INF. Of the 48 patients who did not receive INF (INF− group), 36 were not offered INF without explanation for the clinical protocol deviation, while 12 refused INF. Mean age of the 228 patients treated with parenteral opioids was 12 ± 5 years, 56% were female, and 65% had HbSS (See Supporting Information Table 1 for patient clinical characteristics). Patients in the INF− group had similar gender and hemoglobin genotype, but were older than patients in the INF+ group (13.4 ± 4.0 vs. 11.7 ± 4.5 years, $P = 0.01$).

Triage pain scores were similar in all groups and improved significantly at the time of ED disposition, without a significant difference in the INF+ vs. INF− groups (Supporting Information-Figure 2). Mean time-to-first-parenteral-opioid decreased significantly in the INF+ group compared to historical controls (29 ± 15 vs. 35 ± 18 minutes, $P < 0.01$, $n = 228$) and the INF− group (77 ± 44 minutes, $P < 0.001$; $n = 48$). The ED LOS between the INF+ group and historical controls was similar, but lower in the INF− group. Admission rates were similar in the INF+ group and historical controls but significantly higher in the INF− group (48% and 45% vs. 71% respectively, $P = 0.004$; Table 1).

No adverse events including over-sedation or respiratory depression occurred during the study. The most common side effects included complaints of nasal burning and irritation after administration.

TABLE 1 Clinical outcomes in children with SCD/VOE who received intranasal fentanyl (INF+) compared to those who did not receive INF (INF−) and historical control data

	INF+ (*n* = 180)	INF− (*n* = 48)	Historical data (*n* = 229)	*P*-value
Time-to-first-Parenteral-Opioid (minutes±SD)	29 ± 15[a]	77 ± 44[b]	35 ± 18[c]	*P*< 0.0001
Length of Stay (minutes)	215 ± 86[ab]	197 ± 67[a]	231 ± 95[b]	*P*=0.028
Admission Rate N (%)	86 (48%)[a]	34 (71%)[b]	103 (45%)[a]	*P*=0.004

[a/b/c] Groups with the same letter are NOT statistically different at a $p < 0.05$.

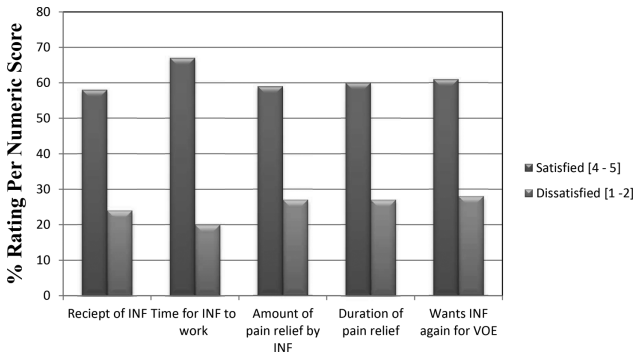

FIGURE 1 Patient/parent satisfaction data in children who received INF

One-hundred-twenty-nine families completed the patient satisfaction questionnaire, and 100 (78%) had received INF. Sixty-one percent of patients (*N* = 61) who received INF were satisfied and would like to receive the treatment again (Figure 1). Families were also more likely to rate their medical care in the ED at a 9 or 10 (on a scale of 1–10 with 10 being the best care received, and 1 being the worse care received) in the INF+ group compared to those who did not get INF (Supporting Information-Figure 3), however this did not reach statistical significance.

All 30 ED nurses queried completed an anonymous nursing questionnaire designed to assess their level of comfort in administering INF in general and to patients with SCD: 27 nurses (90%) had experience delivering INF at some point in their career prior to onset of this INF-SCD initiative, 27 nurses (90%) were comfortable with delivery of INF for any patient in pain and 25 nurses (83%) were comfortable with the delivery of INF for VOE.

Delays in delivery of analgesia for VOE in children with SCD have been reported in the literature,[3] demonstrating a need to seek methods to optimize pain control. INF represents a strategy to allow for more rapid parenteral opioid delivery that circumvents time-delays for IV access. In our study, we were able to adhere to the NHLBI guidelines which recommend delivery of the first dose of parenteral opioids within 30 minutes of triage or 60 minutes of registration in the acute care setting. [5] In a recently published randomized placebo-controlled trial involving children with SCD and moderate-severe pain, subjects randomized to INF had a greater decrease in median pain score at 20 minutes but not at 10 or 30 minutes.[4] This observation suggests that short-acting INF is best used for rapid pain relief as a temporizing bridge during IV access until longer-acting parenteral opioids are provided, as done in this study.

We did not find a difference in admission rates between those who received INF compared to historical controls. However, INF was implemented within a nursing-driven protocol for the assessment and management of pain associated with VOE, which has been shown to improve time-to-administration-of-first-analgesia and percentage of patient visits receiving pain medication within 30 minutes of triage in a pediatric ED setting.[1] Since nurse-initiated protocols were in place within the CHOA ED prior to the INF QI project, mean time-to-first-parenteral-opioid administration was already within the NHLBI-recommended window of arrival. However, inclusion of INF orders into SCD-specific nurse initiated guidelines reduced time even further, to less than 30 minutes, consistent with past observations with INF use in the ED for non-SCD adults and children presenting with pain as well as in SCD.[3,6] A second consideration is that the mean admission rate was already less than 50%, well below the national average; it is possible that further improvement with respect to disposition was not feasible.

The significantly higher admission rate for children who did not receive INF warrants further consideration. It is possible that the patients not treated with INF were experiencing more severe VOE, as more of these children had hemoglobin-SS compared to the INF+ group, and admission decisions were more rapidly made. These children were also older and may possess additional risks for admission not identified by this study design. It is also possible that the associated delay in treatment with parenteral analgesia may have contributed to the increased admission rate, or that high ED volume or acuity led to a delay in care. Regardless, causality of INF use on admission rates cannot be determined without further study.

Adverse events with INF are rare and none were reported during this study. The majority of SCD patients with VOE who received INF was satisfied and wanted to receive INF again during future ED visits for pain. Nurses were also comfortable delivering INF to patients with SCD and pain; no major nurse-related barriers to INF administration were identified.

Ultimately, we found that INF use significantly improved time-to-first-parenteral-opioid dose and was a safe and effective treatment for pain. After this successful pilot study, INF was added to the nurse-initiated SCD-specific protocol for the treatment of moderate-to-severe VOE across the CHOA network that included 3 large pediatric EDs that evaluate over 1400 episodes of SCD/VOE annually. This study adds to the growing clinical experience supporting use of INF as

a strategy to achieve the NHLBI recommendations for rapid delivery of parenteral opioids for children with SCD suffering from VOE in the ED.

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Prevalence of venous thromboembolism diagnosed in emergency department visits by cancer patients and associated healthcare resource utilization in the United States

To the Editor:

Venous thromboembolism (VTE) is one of the leading causes of morbidity and mortality in cancer patients. Most cancer patients are followed and treated as outpatients and symptoms from VTE can prompt emergency department (ED) visits. Data is scarce regarding VTE diagnosed in the ED setting and associated outcomes. We investigated the prevalence of VTE diagnosed among cancer patients in the EDs and subsequent hospital admission rate, mortality, and healthcare resource utilization.

The study cohort was obtained from the Nationwide Emergency Department Sample (NEDS) database, which is the largest nationally representative ED database in the United States. ED visits by patients with at least one cancer diagnosis from 2006 to 2012 were included in our analysis. VTE diagnosis was identified with *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9 CM) codes. The utilization of imaging studies which could lead to diagnosis of VTE was identified using current procedural terminology code. Imaging studies of interests were duplex ultrasound of the extremity veins (DUV), ventilation-perfusion scan (V/Q scan), computed tomography pulmonary angiography (CTPA), and computed tomography of chest with intravenous contrast (CTC). CTC was included because it could detect pulmonary embolisms (PEs) incidentally albeit the study was ordered for other purposes.

The prevalence of VTE among cancer patients during ED visits was estimated. Multivariable logistic regression analysis was used to estimate the effect of VTE status on subsequent hospital admission, mortality risk, and total hospital costs. Higher total hospital costs was defined as greater than the 75th percentile of the study population (> $43 964). A two-sided P value < .05 was considered statistically significant.

There were 6 330 322 ED visits by cancer patients included in our study. The median age was 70 (interquartile range: 58–80) and