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RESEARCH ARTICLE

Improved Management of sickle cell pain crisis in a Pediatric Emergency Department through Use of Intranasal Fentanyl.

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ABSTRACT

Introduction: National Heart, Lung, and Blood Institute recommends giving the first dose of opioids within 30 minutes of presentation to the emergency department for sickle cell disease patients with moderate to severe vaso-occlusive crisis. Intranasal fentanyl has been used extensively and shown to reduce time to the first dose of analgesic, improve pain scores at 20 minutes, and increase the odds of getting discharged from the emergency department.

Material and methods: For phase one of the project, baseline data was collected. The new pain algorithm was introduced at the start of the second phase, which involved giving intranasal fentanyl as the first analgesic for vaso-occlusive crisis in the emergency department. After the intervention, the second analysis compared outcomes with phase one. Wilcoxon-Mann-Whitney tests were used for comparing data between phase one and phase two and Wilcoxon signed-rank tests (paired version) were used for comparing pain scores before and after analgesic.

Results: Visits at phase two had significantly lower hospitalization rate [phase one 53.5% vs. phase two 34.2%(p value 0.005)], more fentanyl use [phase one 1.5% vs. phase two 50.6% (p< 0.001)], less patient-controlled-analgesia (PCA) opioid use after admission [phase one 13.0% vs. phase two 2.53% (p= 0.016)], higher compliance with outpatient visits [phase one 61.3% vs. phase two 98.7% (p < 0.001)], shorter length of hospital stay [phase one 117.6 ± 112.7 hours vs. phase two 68.3 ± 47.2 hours (p-value 0.01)], decrease in the time to first analgesic after coming to the emergency department (phase one 78.2 ± 131.2 minutes vs. phase two 38.3 ± 31.2 minutes (p 0.85)], and decrease in the mean pain score after first medication in the emergency department [phase one 5.48 ± 3.12 vs. phase two 4.46 ± 2.88 (p value 0.021)]

Conclusion: Intranasal fentanyl led to more effective and timely management of vaso-occlusive crisis with improvement in clinical outcomes compared to standard management.

Introduction:

Sickle cell disease (SCD) affects approximately 100,000 Americans. SCD occurs among about 1 out of every 365 African American births, about 1 out of every 16,300 Hispanic American births, and about 1 in 13 African American babies is born with sickle cell trait (SCT).[1] The pathophysiology of the clinical manifestations of the disease is damage to the red blood cell membrane from rigid polymers formed by deoxygenated hemoglobin, thereby activating various abnormal cell-signaling pathways. Clinically, it presents with marked hemolytic anemia, progressive organ damage, vaso-occlusion, and premature mortality, but the most common presentation of the disease is pain or vaso-occlusive crisis (VOC).[2]

Vaso-occlusive crisis is the most common indication for patients with SCD to seek emergency care.[3] It is caused by the entrapment of sickled hemoglobin-containing red blood cells (HbS) in the microcirculation that can lead to ischemia, inflammation, reperfusion injury, and localized tissue damage. Early alleviation of the pain associated with an acute episode may be essential to prevent further tissue damage.[4] Nearly all individuals affected by SCD will experience a VOC during their lifetime. The first VOC may occur as early as six months of age, often presenting as dactylitis, but after that VOCs occur with variable frequency, and the accompanying pain most commonly occur in the extremities, chest, and back.[5-7] Sickle cell pain is worse than postoperative pain and is as intense as terminal cancer pain. Increased frequency and severity of pain episodes are associated with shortened survival.[8]

The National Heart, Lung, and Blood Institute (NHLBI) recommends an initial dose of parenteral opioids within 30 minutes of triage for moderate-severe VOC in the acute care setting.[9] The NHLBI also recommends repeated assessments and doses of opioids every 15 to 30 minutes in the emergency department (ED) until sickle cell pain is relieved or reduced. Adherence to the NHLBI guidelines is associated with reductions in ED length of stay, fewer admissions to the hospital, and improved patient satisfaction.[10,11] Education is the most crucial step in reducing the time-to-first dose for SCD pain.[2] Using alternatives to intravenous administration is an excellent strategy for reducing the time-to-first dose as intravenous line placement can sometimes be delayed owing to surges in the ED or difficulty in obtaining access.[2] Intranasal fentanyl (INF) has been extensively studied and is found to be associated with dramatic reductions in the time to first and second dose of analgesic and low hospitalization rates.[10,12] First-dose subcutaneous opioids (an approach recommended by the NHLBI guidelines) and first-dose oral opioids are also excellent strategies to mitigate delays in intravenous line placement.[13,14]

Hypothesis:

Intranasal fentanyl in acute vaso-occlusive crisis in sickle cell patients can lead to fewer rates of hospitalization, faster pain relief, shorten the duration of stay in hospital as well as increase the rates of discharge from the ED.

Setting:

This project was implemented at Ascension Sacred Heart Hospital, Pensacola, through the

Studer Family Children's Hospital Emergency Department.

Materials and Methods:

A retrospective chart review of electronic health records was conducted for SCD patients attending the ED with pain crisis from September 2018 to September 2021. The records were retrieved from the database of Cerner One electronic health record system with selection of charts based on ICD-10 codes for sickle cell pain crisis. Patient characteristics, including patient demographics, outpatient pain medications used and pain location, were recorded. Additionally, medical treatment characteristics, including initial pain medication administered on arrival to the ED, time to first dose of opioid, initial, and subsequent pain scores, and outcome measures including number of hospitalizations, length of stay in hospital and number of patients discharged from the ED, were also recorded. The collected phase one data was analyzed to establish a baseline of study outcomes while utilizing the existing pain management algorithm in the ED. In the second phase, we created a new algorithm to manage sickle cell pain crisis in the pediatric emergency department featuring intranasal fentanyl (INF). As a part of this algorithm, the first step was to use INF upon arrival at the ED if they met the criteria for its use, then after INF, attempt intravenous fluids and intravenous analgesics. We compared the outcomes including hospitalization rates, use of INF, PCA opioid use after admission, compliance with outpatient care, length of hospital stays, time to first analgesic in the ED and pain scores for phase one vs. phase two. Wilcoxon-Mann-Whitney tests were used for comparing data between phase one and phase two and Wilcoxon signed-rank tests (paired version) were used for comparing pain scores before and after analgesic.

Results:

In the first phase of the project, 50 unique patients with 200 visits were identified, and 33 unique patients with 79 visits were identified in phase two of the project. Wilcoxon-Mann-Whitney tests were used for comparing data between phase 1 and phase 2 and Wilcoxon signed-rank tests (paired version) were used for comparing pain scores before and after analgesic.

There was a mean age of 10.09 (S.D. 5.3), 47.0% were female, 96.4 were African American with no differences in demographic variables in phase one vs. Phase 2. There were no differences in type of sickle cell disease with SS and SC comprising 60.2% and 27.7% respectively. There were 10.8% with Sickle-Beta-thalassemia with no differences between phase one vs. phase two.

The outcome variables were compared between the two phases (as shown in Table 1). There were no differences in initial pain scores with phase one pain score of 6.88 (S.D. 3.08) and phase two pain score of 7.61 (S.D. 2.42). Visits at phase two had significantly lower hospitalization rate [phase one 53.5% vs. phase two 34.2%(p-value 0.005)], more INF use [phase one 1.5% vs. phase two 50.6% (p-value < 0.001)], less patient controlled analgesia (PCA) opioid use after admission [phase one 13.0% vs. phase two 2.53%(p-value 0.016)], and higher compliance with outpatient visits [phase one 61.3% vs. phase two 98.7% (p-value < 0.001)], shorter length of hospital stay [phase one 117.6 ± 112.7 vs. phase two 68.3 ± 47.2 hours (p-value 0.01)], decrease in the time to first analgesic after coming to the ED (phase one 78.2 ± 131.2

vs. phase two 38.3 ± 31.2 minutes (p-value 0.85)], and decrease in the mean pain score after first medication in the ED [phase one 5.48 ± 3.12 vs. phase two 4.46 ± 2.88 (p-value 0.021)]

Table 1. Comparison between phase 1 and phase 2

Outcome variable	Phase 1	Phase 2	P value
Hospitalization	53.5%	34.2%	0.005
Length of stay	117.6 ± 112.7 hours	68.3 ± 47.2 hours	0.01
Fentanyl use	1.5%	50.6%	<0.001
PCA opioid use after admission	13%	2.5%	0.016
Compliance with comprehensive care	61.3%	98.7%	<0.001
Initial pain score	6.88 ±3.08	7.61 ± 2.42	0.124
Time to first analgesic after arrival to ED	78.2 ± 131.2 minutes	38.3 ± 31.2 minutes	0.85
Pain score after first pain medication in ED	5.48 ± 3.12	4.46 ± 2.88	0.021

Discussion:

In this study, there were improvements in outcomes in phase two with INF vs. standard management for vaso-occlusive crisis. There was no difference in the amount of pain measured on admission but with INF, in phase two, there was less pain on the second pain score measured after treatment. As noted, there was also less utilization of health care resources including fewer admission rates, use of PCA, shorter length of hospital stays, and even better outpatient visit compliance. These improvements indicate that INF should be considered a valid treatment alternative to standard care using IV opioids. It is likely that INF is better and more timely in that it doesn't require insertion of an intravenous line. These results are supported by review of the literature as discussed below.

Vaso-occlusive crisis, often referred to as a pain "crisis", is the hallmark clinical presentation of SCD, leading to approximately 70% of hospitalizations after ED presentation.[15] Unrelieved pain not only leads to negative consequences on the quality of life of these children and young adults but is also associated with early mortality in these patients.[16,17] Suboptimal pain management in SCD patients is often associated with caregiver's concern for creating opioid dependence, and underestimating the extent

of pain in these patients.[18] Prevalence estimates for opiate addiction among patients with SCD range between 0.5% to 8% compared to patients with chronic pain syndromes with opiate addiction rates of 3% to 16%.[19,20] As opposed to conventional pain management in SCD using IV and, or oral opioids in the ED, there is increasing evidence of benefit with using IN opiates (fentanyl, sufentanil, and diamorphine) for the management of VOC in SCD.

A randomized controlled trial done by Barrett MJ et al. found INF is non-inferior to IV morphine with a significance of 0.05.[21] Another randomized, double-blind, placebo-controlled trial done by Daniel M.Fein et al. found a statistically significant reduction in pain score at 20 minutes compared to the placebo group.[22] Study by Hugo Paquin et al. found that the use of INF is associated with a significant reduction in the time to the first dose of the opiate and the number of intravenous line placements in the ED.[23] A large multicenter and cross-sectional study conducted at 20 academic pediatric emergency departments in the US and Canada found that children who received INF had nearly nine-fold adjusted odds of discharge from the ED compared to those who did not. This study also found that there was a greater likelihood of receipt of parenteral opioids ≤30 min after presentation to the ED compared to children who did not receive INF. Additionally, children who received INF were more likely to receive their first parenteral opioid ≤ 60 min after presentation to the ED compared to children who did not receive INF at the 10 sites that used INF.[24]

While the timing of opioid administration is considered a quality indicator for pain episodes in SCD,[25] ED crowding, staffing shortages, and delays in obtaining IV access may contribute to delays in administering IV opioids to SCD children with VOE.[26, 27] Rees et al. reported a median time to IV placement from ED arrival of 52 minutes,[28] which represents an important bottleneck to rapid delivery of IV opioids. Consequently, INF provides an excellent approach to rapidly treat for VOC as recommended by recent NHLBI, American College of Emergency Physicians, and American Society for Hematology guidelines.[29-31] Compared with other routes of drug administration, the IN route has several advantages, including rapid pain relief, higher patient satisfaction, relatively painless, inexpensive, convenient, and easy to deliver with minimal training, and more efficient use of resources.[32] When used in analgesic doses, fentanyl has minimal sedative and hemodynamic effects.[33]

Although many studies have shown the benefit of INF in the management of VOC in sickle cell disease patients, it is still not being utilized in many EDs. The study by Rees et. al, 75% of the EDs had access to INF, but only 50% of them used it in their VOC pain management procedures.[24] In a separate cross-sectional survey given to ED physicians that had INF available, 41.9% of providers were reluctant to administer INF to patients due to parental reluctance, and 25.7% were reluctant due to a lack of clear guidelines for use.[33] Therefore, in addition to a prospective study assessing the efficacy of upfront INF in the treatment of pain in children with SCD, both provider and care-giver education will be needed for successful implementation, particularly given fentanyl's association with illicit drug use.

Limitations of this study:

There are several limitations to this study: First, only 50.6% of patients in phase two were managed according to the new protocol. If compliance was higher, the outcomes likely would have been even more striking. Second, these results reflect the experience of one institution with a small sample size. The results may not be generalizable to the population at large. There also may be recording errors in some of the chart data. Finally, this was not a controlled study but rather a before and after analysis which may be subject to confounding variables that may have influenced the outcomes presented here. There needs to be a controlled blinded clinical trial conducted on a larger population to confirm these findings.

Conclusion:

Early alleviation of the pain associated with an acute vaso-occlusive crisis is essential to prevent further tissue damage. Effective and timely management of vaso-occlusive crisis of children with intranasal fentanyl was found to result in significantly better outcomes than with standard therapies.

Conflicts of Interest:

None

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