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Original Article

Oral morphine protocol evaluation for the treatment of vaso-occlusive crisis in paediatric sickle cell patients

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Abstract

Background: Vaso-occlusive crisis (VOC) is one of the most frequent causes of emergency visit and admission in children with sickle cell disease (SCD).
Objectives: This study aimed to evaluate whether the implementation of a protocol promoting the use of oral morphine as a primary intervention has led to improved care of SCD.
Methods: We performed a retrospective chart review of patients with SCD who presented to the emergency department (ED) and hematology outpatient clinic (HOC) with VOC, in the year pre and postimplementation of the protocol. The primary outcome was the hospitalization rate.
Results: The protocol resulted in a significant 43% reduction of hospitalization rate (95% confidence interval [CI] −53.0, 26.5). Results also showed a 35% increase in the use of oral morphine as first-line opiate treatment (95% CI 17.9, 45.2), a 28% increase in the use of pain scales (95% CI 17.3, 43.2) and a 30% net increase in patients eventually not requiring intravenous (IV) line placement (95% CI 16.0, 39.9). While we did observe an overall decrease in length of stay in ED of -55 min (95% CI −100.6, −12.0), there was a nonsignificant decrease of 7 minutes (95% CI −26, 3) in the opiate administration time.
Conclusions: This study validates the use of our oral morphine protocol for the treatment of VOC by significantly reducing the admission rate and decreasing the number of IVs.

Keywords: *Emergency department; Hematology; Pain; Protocol; Sickle cell disease.*

Sickle cell vaso-occlusive crisis (VOC) is the most frequent cause of emergency room visits and hospitalizations in children suffering from sickle cell disease (SCD) (1–3). While SCD mortality in children has significantly decreased over the past 20 years (4), VOC is still associated with significant morbidity (5–7). In addition to fast pain relief, rapid assessment of the SCD patient's pain is crucial since VOC may be associated with other life-threatening complications (8). Delays in treatment may also be associated with greater difficulty in reaching quick and adequate pain control (9–11), which may lead to longer and more frequent hospitalizations and further morbidities, including the development of chronic pain syndromes.

Many treatment protocols (12–15) are currently used for the treatment of VOC. The Canadian consensus statements (16,17) suggest a rapid evaluation of pain, to eliminate other associated symptoms and conditions, using a graded pain scale. Hydration should be instituted early, either orally or via intravenous (IV) line. Pain control should rely on early initiation of treatments, guided by home therapies and previous response to medications, as well as frequent re-evaluation. Despite these recommendations, many protocols still use oral morphine only as a bridge to IV medications. Indeed, some have suggested that the first dose of opiates may be given orally (PO) (18), and transitioning to IV should be based on response, aiming for the

first dose to be given within 15 to 20 minutes of arrival to the emergency department (ED) (19). Adjunct therapies should also be initiated if not already done at home or on a chronic basis (20). Disposition of the patient should be decided within 2 to 8 hours (19).

Prior to 2013, patients with SCD presenting to our local ED with a pain episode were treated mostly with IV hydration and IV morphine, in adjunction to regular PO acetaminophen and/or ibuprofen as first-line treatment and most of them were admitted. In 2012, a group of paediatric hematologists, paediatric emergency physicians, paediatricians, pharmacists and nurses with an interest in pain management for patients with SCD created a group named DrepaNoPain. This group reviewed the treatment protocol for acute pain management in SCD patients, and proposed a new standardized preprinted order (SPPO) based upon a review of recent literature (16,21–24). This protocol was implemented in both the ED and hematology outpatient clinic (HOC). This protocol differs from others previously published by advocating the sole use of oral morphine when possible as treatment, instead of IV opiate, hoping for faster pain relief and avoiding potentially unnecessary IV access and admission. The primary objective of this study was to evaluate whether the implementation of such protocol reduced the rate of hospitalization comparing the cohort of SCD patients presenting to the ED and HOC pre and postimplementation of the SPPO. We also aimed to evaluate if the oral route was eventually preferred to IV administration, and if this led to quicker opiate administration time and a decrease in IV therapies.

METHODS

Study design

This is a single centre retrospective chart review of patients with SCD seen in the ED and HOC for VOC. The institution's review board approved the study.

Study setting and population

The study includes patients with SCD who presented to the ED and HOC with VOC requiring treatment, in the year pre (January to June 2012) and post (January to June 2014) implementation of the SPPO. This new preprinted order was implemented in the spring of 2013 and included informative sessions on VOC treatment for physicians and nurses. Dates were chosen outside of the implementation period (spring-summer 2013) to assess correctly both pre and postperiods (washout period).

The study took place in an urban, tertiary academic centre with more than 75,000 ED and 6,500 HOC visits per year, of which a third are for SCD patients. Patients requiring urgent care, such as for pain or fever, are seen directly in the hematology clinic during weekdays. Patients are seen in the ED after HOC opening hours or during weekends. When discharged from the ED, follow-up is ensured by phone or by visit in the HOC. As of June 2017, a cohort of 340 patients with SCD is regularly followed by the hematology service, through a dedicated SCD program (25) led by two paediatric hematologists and two dedicated SCD nurses. Over the last few years, efforts have been made to optimize pain management at home. Most families have personalized pain management plan for home which includes PO morphine. All patients seen for urgent care of pain crisis were included in the study. Patients who presented with both fever and VOC were excluded, given that they are more likely to require IV therapies and be admitted. Patients with acute chest syndrome were excluded. Fever was defined by a temperature above 38°C. Acute chest syndrome was defined by a new infiltrate on a chest radiograph.

Study protocol

The new evidence-based treatment protocol advocated for oral hydration, acetaminophen, ibuprofen and PO morphine as first-line treatments, aiming at reducing IV procedures, hoping for a faster opiate administration time. Oral rehydration was done at a rate of 60 mL every hour for patients 10 to 20 kg, 80 mL every hour for patients 20 to 40 kg and 100 mL every hour for patients more than 40 kg.

Acetaminophen and ibuprofen doses were 15 mg/kg/dose (maximum of 975 mg/dose) and 10 mg/kg/dose (maximum of 600 mg/dose), respectively. The protocol also encouraged the use of pain scales for pain evaluation pre and postopiate doses, using the EVENDOL (EValuation ENfant DOuLeur) (26) scale for children under the age of 4 years old, and the Oucher (27,28) scale for children aged 4 years and older. As stated in our protocol, for a patient to receive opiate, he/she must have a significant pain, graded over 5/10 on the Oucher pain scale. Patients meeting these criteria were then given a dose of PO morphine unless the treating physician decided otherwise. Following the first opiate dose, patients were treated with subsequent opiate doses if their pain remained over 5/10. Subsequent doses were given orally if the patients' pain had improved, but were given IV if their pain had remained unchanged or increased. Initial oral morphine dose was 0.3 mg/kg/dose (max 15 mg/dose). The breakthrough dose of oral morphine at 45 minutes postinitial dose was 0.15 mg/kg/dose (max 5 mg/dose) if pain was improved but still above 5/10 (Oucher scale) or 7/15 (Evendol scale), but was 0.2 mg/kg/dose (max 10 mg/dose) if pain score was unchanged. Forty-five minutes following the breakthrough dose, patients were transitioned to IV morphine if their pain was still above 5/10 (Oucher scale) or 7/15 (Evendol scale), but were discharged with home oral morphine if their pain had decreased below these thresholds. Pre and postadmission criteria were the same, and included oral treatment failure, need for IV opiates, chest pain, tachypnea, neurological symptoms and patient less than 6 months. Since there was no attempt at prioritizing non-IV opiates in the preperiod, most patients were admitted given requirements for IV opiates.

Data collection

All identified charts from ED and HOC databases were evaluated by two data abstractors not blinded to the study objectives using a standardized excel datasheet. Subjects were obtained by searching patients with a diagnosis of VOC. The chart reviewers, a paediatric emergency resident and a research assistant, were formally trained by one of the supervisor and kappa score ≥0.80 was needed for data abstraction. All data elements were abstracted from the ED and HOC medical record.

A structured chart review was used to abstract all data, including the following outcome variables: time of registration, time of triage in ED, time of physician assessment, time of discharge from ED or HOC, time and route of administration of first opiate dose, as well as all subsequent doses, and disposition of the patient. Time to first opiate dose was calculated by subtracting the time of first opiate dose from the time of registration. It is important to note that all patients with SCD and pain are triaged in ED as Canadian Triage Acuity Scale (CTAS) category 2 (29) at our centre, giving them the highest priority outside of patients brought to the crash room with life-threatening situations. Moreover, our protocol recommended an initial dose of 0.3 mg/kg/dose for PO morphine (maximum 15 mg/dose) and 0.1 mg/kg/dose for IV morphine (maximum 10 mg/dose). Hydromorphone was the substitute drug if patient was known to be morphine intolerant.

Other variables abstracted included demographics (age, gender, sickle cell phenotype), and use of hydroxyurea. We also calculated the baseline hemoglobin level for all patients by calculating the mean of the 3 hemoglobin values prior to each visit. Return to ED or outpatient clinic at 72 hours and at 28 days was also noted, either for ongoing VOC or scheduled follow-up appointment. If a patient visited the ED or HOC multiple times during the study period, each visit was recorded as a new event and analyzed separately.

Data analysis

Information was recorded on an excel data spreadsheet. P value of less than 0.05 was defined as significant. Each variables normality distribution was tested using D'Agostino-Pearson test using MedCalc (v 13.1.2). Proportions were compared by chi-square, and medians were compared by Mann–Whitney test using SPSS version 20. Confidence intervals for the difference were reported.

Sample size calculation

We estimated that 35 visits per arm would be sufficiently powered to detect at least a 30% rate reduction of admissions, with a power of 80% and a significance of 0.05.

RESULTS

A total of 147 visits of patients with VOC were seen in ED or HOC during the study period and all were included in our study: 72 visits in pre, and 75 visits in post, with an overall mean age of 9.4 ± 5.3 years. Individual patient characteristics are presented by period in Table 1.

In total, 59 of 72 (82%) patients were admitted in pre versus 29 of 75 (39%) in postperiod: a difference of −43% (95% confidence interval [CI] −53.0, −26.6). Admission rates decreased by 48% (95% CI −61, −31) in the ED, and decreased by 39% (95% CI −59, −11) in HOC. Specifically, for patients with the SS phenotype, admission rates decreased by 40% (95% CI −53, −24). None of the patients discharged in pre returned to hospital within 72 hours of their VOC, compared to 3 of 46 (7%) in post. Of those three patients, two eventually required hospitalizations; the last patient was discharged after being treated with IV opiates. We had no return at 28 days in both groups. Comparative results for study objectives are shown in Table 2. The new protocol increased the use of oral morphine and pain scales and it decreased the number of IVs inserted and overall length of stay (LOS). It had however no effect on time to first opiate dose. The characteristics of the ED visits are presented in Table 3.

Although the protocol favoured the use of PO medication, patients seen in the ED continued to have IV access, even in patients that received PO medications only, with 17 of 52 (33%) patients having had an IV and only PO or no medications in postperiod. In these cases, IVs were placed for IV hydration, although PO hydration was advocated for in the SPPO. In contrast, the number of IV access placed in the HOC significantly decreased in the postperiod, with only 2 of 23 (9%) patients with IVs having their pain treated with only PO or no medications.

Table 1. Patient characteristics per study period

	Preperiod	Postperiod
Number of visits	72	75
ED	47	52
HOC	25	23
Number of patients	48	49
Age, years (IQR)	6.6 (5.0, 15.7)	9.6 (5,14)
Male, n (%)	43 (60)	37 (49)
Sickle cell phenotype, n (%)		
SS	57 (79)	49 (65)
SC	13 (18)	23 (31)
SB°Thal	1 (1)	2 (3)
SB+Thal	1 (1)	1 (1)
Hydroxyurea, n (%)	22 (31)	36 (48)
Opiates received, n (%)	61 (85)	61 (81)

Data presented represent individual patients and are organized by study period.

years: years (median)

ED Emergency department; HOC Hematology outpatient clinic; IQR Interquantile range; n Number; SS Hemoglobin SS; SC Hemoglobin SC; SB°Thal Hemoglobin SB°Thal; SB+Thal Hemoglobin SB+Thal.

Table 2. Comparatives results for study objectives

	Preperiod (72 visits)	Postperiod (75 visits)	Δ (95% CI)
Hospitalization rates, n (% of total)	59 (82)	29 (39)	−43% (−56, −28)
SS, n (% of SS)	48 (84)	20 (41)	−40% (−53, −24)
SC+ SB, n (% of SC+SB)	10 (67)	9 (35)	−2% (−13, 9)
PO Morphine for first opiate dose, n (%)	16 (22)	43 (57)	38% (23, 52)
Time ins. to first opiate dose, min (IQR)	95 (77, 141)	88 (70, 120)	−11 min (−26, 2)
Number of patients with IV inserted, n (%)	65 (90)	45 (60)	−30% (−43, −17)
Pain scale use pre-first opiate dose, n (%)	17 (24)	39 (52)	28% (13,42)
LOS, min (IQR)	334 (210, 440)	279 (211, 364)	−43 min (−92, −1)
Return at 72 h, n (%)	0 (0)	3 (4)	4% (−2, 11)
Return at 28 days, n (%)	0 (0)	0 (0)	0% (−5, 5)

Data presented represent individual patients and are organized by study period.

Ins Inscription to emergency department; IV Intravenous; LOS Length of stay; n Number; PO Per Os.

Table 3. ED visit characteristics

	Preperiod	Postperiod
Time ins. to triage (min)	15 (8,22)	13.5 (8,19)
Time triage to MD (min)	16.5 (9, 24.5)	14.5 (8,27)
Time MD to first dose (min)	62 (39, 87)	63.5 (41, 93)
Time ins. to first dose (min)	87 (76, 117)	94.5 (70.5, 121.5)

Data presented represent individual ED visits and are organized by study periods.

All reported times represent the median ± IQR.

ED Emergency department; Ins Inscription to emergency department; LOS Length of stay; MD Medical doctor.

DISCUSSION

Our study demonstrates a change in practice at our centre following the introduction of a PO morphine protocol using a SPPO, which was successful at drastically reducing the number of admissions. Indeed, we were able to show that our SPPO, with adequate informative sessions, allowed knowledge translation and permitted to a larger proportion of SCD patients with VOC to be effectively treated as outpatient. As per NIH recommendations, working closely with a day treatment centre allowed for patients with controllable pain to be followed as outpatients. Our better understanding of their pain and our growing comfort with oral opiates allowed for a significant number of patients to be treated without the use of IV medications and hydration, though achieving adequate pain control, which is different from other studies evaluating similar protocol (30). Thus, this represents a winning combination to avoid unnecessary hospitalization. With this protocol, treatment goals shifted from pain eradication to pain control, as patients whose pain was stable or significantly improved on PO medications were treated as outpatients. Although not a goal of our study, the high proportion of patients requiring treatment with opioids show that such medication remains important in the management of SCD, despite the current desire to replace opioids with nonopioid analgesics (31).

Moreover, this change in practice was further supported by an increase in use of oral morphine as first-line therapy. A study by Jacobson, cited in the Cochrane review on pain management for SCD, showed no significant difference in the mean overall pain scores, frequency of rescue analgesia and of adverse effects, between PO and IV morphine (18,32). Favouring PO versus IV opiates also was found to decrease the admission rates (30), although our decrease in hospitalization rates was more significant than the one reported by Campos. The paper by Campos described a protocol using PO morphine as well as IV morphine and had shown promising results by decreasing their hospitalization rates and length of stay in ED. However, as stated, their protocol did not have the possibility of only receiving oral therapies. Thus, whenever possible and guided by the physician's judgement, it seems that oral morphine is an appropriate choice.

Additionally, a study by Ender et al. showed that the use of a clinical pathway improved management of sickle cell VOC in the ED, by decreasing the time interval to first analgesic (20). While we acknowledge that the NIH recommendations of 15 to 20 minutes to first analgesic may be very difficult to achieve in our ED, we thought that the introduction of a protocol using PO morphine as first-line therapy would allow for more rapid administration of opiates. A more realistic goal suggested by Wang et al. as quality of care indicators for treatment of VOC was administration of opiate 30 minutes from triage or 1 hour from registration (24). Our delay of about 90 minutes in each arm falls outside of these recommendations, despite the use of a clinical pathway, but also leaves room for improvement. As shown in Table 3, we can see that most of our delay in treatment

results from the time the MD sees the patients until the first dose is given. This is likely explained by the functioning of an academic centre, where residents see patients first before reviewing cases with an attending physician. ED overcrowding, which affects the work and availability of nurses, may also play a role.

The overall decrease in IV line placements observed in our study is of great importance for these patients, who may require multiple attempts prior getting a successful IV procedure. However, the fact that the ED had more unnecessary IV procedures could potentially explain the persistent delays in time to first opiate dose in the postprotocol period, if nursing focused on the need for IV line placement instead of pain control by other means. Our results also showed opportunity for improvement given that an IV was placed for IV hydration only in 33% of patients with IV, despite protocol recommendations. This shows that changes in practice may take longer to take place and that ongoing education and reminders about the protocol are necessary. Empowering the nurses to challenge the need for an IV may be a solution when no IV medications are prescribed.

Following the institution of our protocol, pain score pre and postopiate administration were increasingly recorded, showing that a standardized protocol increased the use of pain scales. Although the use of our new protocol and SPPO favoured documentation and assessment of pain scores, these were still documented in only about 50% of patients at first evaluation. Our study encourages us to continue our efforts to promote the use of pain scale and adequate documentation. These measures will allow us to study the impact of protocols targeting pain management.

Despite a high number of successful discharges at initial visit, it was important to evaluate if those patients sent home were adequately treated in the postperiod. Given that patients preprotocol were almost exclusively admitted, the increase in patients returning for pain or followed in the hematology clinic does not come as a surprise, although the return rate was low. The overwhelming difference in the hospitalization rate is nevertheless in favour of using our protocol as a choosing wisely initiative.

LIMITATIONS

Limitations of our study include the use of a retrospective chart review. However, recording of opiate route and time of administration was very well documented and present for all our patients. Moreover, time of registration, triage, MD assessment and time of discharge from ED are all electronically entered through our ED system, which made abstraction very reliable. Also, the lack of consistent data on home opiate intake prior to visit did not allow us to analyze its effect on pain treatment in the ED and need for hospitalization. Indeed, the retrospective nature of our study does not allow us to have consistent data on home opioid intake, especially on timing of intake. However, a majority of patients had not taken any opioids prior to their visit. It is also possible that for some patients, the persistence of high pain despite home opioid intake would have influence the physician towards IV medications as a failure of oral medications. Moreover, differences were noted when comparing the pre and postgroups. The higher proportion of patients with the SC phenotype in the postperiod could potentially influence the hospitalization rates. Similarly, the higher proportion of patients on hydroxyurea in the postperiod, explained by the fact it had become standard therapy around the postperiod, could have a similar effect. The access to HOC was not assessed as a possible factor in decreasing hospitalization rates since its capacity, including opening hours and the composition of the hematology team, had not changed over both periods. Furthermore, the low frequency at which pain scores were recorded in the medical charts does not allow us to comment on the efficacy of PO versus IV morphine. However, the decrease in hospitalization rate suggests that PO morphine was effective in controlling pain. Regarding the delays in initiating therapy, we were unable to measure the contribution of other potential factors such as high acuity cases, ED overcrowding or opiate distribution delays by pharmacy in prolonging time to first opiate dose.

CONCLUSION

This study validates the use of our protocol promoting oral morphine for the treatment of sickle cell VOC, by showing a significant reduction in hospitalization rates. Although a reduction in time to first opiate dose was not seen in the post protocol period, it decreased the number of painful IV procedures. In order to meet quality of care indicators, new strategies will be conducted with the aim of reducing time to first opiate dose.

ARTICLE SUMMARY

Why is this topic important?

Sickle cell VOC is the most frequent causes of emergency room visits and hospitalizations in children suffering from SCD. Multiple protocols exist for the treatment of these crises, and most agree on an initial trial of oral medications when acceptable, which often only serve as a bridge to IV medications and treatments. Although many say that oral treatment is feasible, the majority still choose IV therapies.

What does this study attempt to show?

In view of improving the care of our patients with SCD presenting with VOC in the outpatient setting, the primary objective of this study was to evaluate if the implementation of a protocol suggesting oral morphine has led to improved care, translated by a reduced rate of hospitalization, comparing the cohort of SCD patients presenting to the ED and HOC pre and

postimplementation of the standardized order. We also aim to evaluate if the oral route was favoured for morphine administration, and if this led to quicker opiate administration time, less IV procedures and increased use of pain scales.

What are the key findings?

This study shows that a protocol favouring oral medications and therapies can decrease hospitalization rates and IV procedures while still efficiently treating the pain of VOC.

How is patient care impacted?

Patients have since seen a better utilization of outpatient resources, as well as required less painful IV procedures.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent: Waived consent was obtained from all individual participants included in the study.

Contributors' Statements: EDT, NR, YP and M-JDB conceptualized and designed the study. HP designed the data collection instruments, coordinated and supervised data collection and drafted the initial manuscript. BB carried out the statistical analyses. All authors reviewed and revised the manuscript, and approved the final manuscript as submitted.

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Compliance with Ethical Standards

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