Original Article

Assessment of patient-controlled analgesia versus intermittent opioid therapy to manage sickle-cell disease vaso-occlusive crisis in adult patients

ABSTRACT

Background: Vaso-occlusive crisis (VOC) is one of the acute complications of sickle-cell disease (SCD). Treatment mainly relies on hydration and pain control by analgesics. The specific aim of this study was to assess potential health outcomes within the first 72 h of admission between intermittent and patient-controlled analgesia (PCA) by opioids among VOC patients.

Methods: A retrospective chart review study was conducted to determine SCD patients with VOC. Using the hospital electronic system, the following data were collected: patient's age, gender, blood pressure, heart rate, respiratory rate, oxygen saturation, and pain score on admission and daily for 3 days as well as the cumulative opioid analgesic dose for 72 h which is reported as morphine equivalent.

Results: One hundred and seventeen patients were screened over a period of 5 years. Of those, 99 (84.6%) met the study inclusion criteria, and 18 patients (15.4%) were excluded from the study. During the first 72 h of admission, a significant reduction in pain score was observed in patients on intermittent intravenous (IV) administration compared to those in the PCA group ($P < 0.0004$) where the mean pain scores were 3 and 5, respectively. The total amount of morphine administered over 72 h of admission was significantly higher in PCA group (777 ± 175 mg) as compared to the intermittent IV administration group (149 ± 74 mg) ($P < 0.000003$). Clinically significant hypotension or respiratory depression was not observed in both groups over the 72 h of admission.

Conclusion: During the first 72 h of admission, intermittent IV administration of morphine was more effective than PCA infusion in pain control.

Key words: Anesthesia; morphine; opioids; sickle-cell disease

Introduction

Sickle-cell disease (SCD) is one of the most common hematologic genetic diseases and has been identified as a major public health problem by the World Health Organization (WHO). Normal adult hemoglobin is composed of two α-globin chains and two β-globin chains (α 2 β 2). A single substitution of the amino acid valine to glutamic acid at position six of β-globin chain is responsible for the production of a defective form of hemoglobin called sickle

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hemoglobin.[1] On deoxygenation, molecules of this abnormal hemoglobin will polymerize to form long polymers that physically deform the red blood cell into crescent or sickle shape and ultimately obstruct blood flow.[2]

The highest incidence of SCD is seen in those with African heritage, but it may affect persons of India, Saudi Arabia, Mediterranean, South and Central America, and Caribbean ancestry. It is estimated that about 200,000 infants are born with this disease in Africa.[3] In the United States, it affects about 72,000 people, and 2 million are known to be trait carriers.[2] In Saudi Arabia, the prevalence of trait carriers is estimated to range from 2% to 27%. The Eastern Province had the highest prevalence of SCD by up to 2.6% followed by the southwestern province.[4,5]

Vaso-occlusive crisis (VOC) is one of the complications of SCD. It is described as acute painful episodes caused by sickled RBCs that adhere to the vascular endothelium producing microcirculation occlusions that would lead to tissue ischemia and subsequent damage of the tissues.[6] Although the majority of such painful episodes can be managed at home, acute episodes crisis is a common reason for emergency department (ED) visits and hospitalizations among SCD patients. It has been shown that 5.2% of patients with SCD had 3–10 episodes of severe painful crisis every year.[7] Mortality in SCD patients was at highest rate during the course of painful crisis episodes. Circumstances of death in 209 patients who were over 20 years of age were examined in the cooperative study of sickle cell disease. Forty-five deaths (22%) occurred during the pain episode, and of these events, 20 were complicated by an episode of acute chest syndrome.[8]

No updated evidence-based guidelines exist for the management of acute pain episodes associated with SCD. However, the management of acute pain episode is merely supportive and includes bed rest, hydration, oxygen, and analgesia.[6,9-11] The use of analgesia during the VOC should follow a three-step ladder recommended by the WHO for the management of cancer-related pain.[10] For initial treatment at home, nonopioid analgesics, such as acetaminophen and ibuprofen, are recommended and are often adequate for control of mild pain. As the severity of pain increases, weak opioids (codeine and oxycodone) are best used to manage moderate pain either as monotherapy or in combination with acetaminophen. Pain that is significantly severe to require ED visits should be managed with intravenous (IV) administration of opioids.[6,9-11]

Patient-controlled analgesia (PCA) is one of the most common methods for providing continuous infusion of opioids in an inpatient setting. This method gives the patients the power to reduce their pain utilizing a computerized pump. PCA has been studied for its efficacy and safety in oncology and postoperative patients.[12,13] A meta-analysis by Walder *et al*.[14] evaluated 32 randomized controlled trials to compare IV PCA to the conventional controlled analgesia through intramuscular, IV, or subcutaneous routes. They found that PCA is slightly more effective than the conventional approaches. They reported fewer postoperative pulmonary complications with PCA compared to conventional approaches, and the amount of consumed opioids was not significantly different between the two methods. In addition, Wasylak *et al*. found out that IV PCA reduces morbidity and time to hospital discharge when compared to IM analgesia.[15]

Until recently, limited information is available regarding the use of PCA in SCD patients with VOC. Only one small trial has studied the safety and efficacy of morphine administered by either intermittent injection or PCA to adult patients in the ED with pain due to VOC. The patients in this trial were randomly assigned to be given morphine by either intermittent IV injection or by PCA. They found out that the total number of administered morphine doses was significantly less in the intermittent IV group (6.5 ± 2.6) when compared with the PCA group (29.7 ± 16.6) ($P = 0.0006$). However, the total amount of administered morphine was not significantly different between the groups (28.8 ± 13 mg for the intermittent injection group and 35.5 ± 23.5 mg for the PCA group with $P = 0.623$). The decline in pain with time was not significantly different between the two treatment groups ($P = 0.661$).[16]

Since the patients can titrate themselves to the level of analgesia, PCA may therefore be an interesting alternative approach. Hence, we conducted a retrospective observational study in which we compared the pain intensity and pain relief using either PCA or intermittent opioid therapy in addition to investigating prevalence of cardiovascular and respiratory adverse events in SCD patients with VOC.

Methods

A retrospective cohort study was conducted at King Abdulaziz Medical City - Central Region, a tertiary care hospital which has bed capacity of more than 800 beds in the city of Riyadh, Saudi Arabia, after granting approval from the Institutional Review Board. Inclusion criteria include men and women aged 14 years old and above who were admitted to hospital secondary to VOC necessitating treatment with IV opioid either by intermittent IV injection or continuously through PCA for 72 h or more. A chart review was conducted to determine patients with VOC during the period from

January 2010 to December 2014. Patients were excluded from participation in this study if they have a history of alcohol or drug abuse, allergic to morphine, pregnant, or admitted for <72 h. The following data were collected using the hospital electronic system: patient's age, gender, blood pressure, heart rate, respiratory rate, oxygen saturation, and pain score on admission and daily for 3 days as well as the cumulative opioid analgesic dose for 72 h which is reported as morphine equivalent as shown in Table 1. Data on administered opioid were collected electronically and doubled checked from patients' records. Average pain score, blood pressure, heart rate, and respiratory rate were recorded. All data were recorded without patient identifiers to maintain their confidentiality. Pain intensity was evaluated by using a numerical scale from 0 to 10, and defined as follows: mild pain; if reported pain intensity is between 1 and 2, moderate pain; if reported pain intensity is between 3 and 6, and severe pain; if reported pain intensity is between 7 and 10. An adverse drug reaction was defined as hypotension (systolic blood pressure <90 mmHg) and/or respiratory depression (respiratory rate <12 breaths/min).

Statistical analysis

Data were analyzed using SAS 9.2 (SAS Institute Inc., NC, USA). Baseline demographics and clinical characteristics are summarized and reported using descriptive statistics. Interval variables such as age are summarized and reported in terms of mean and standard deviation. Categorical variables such as gender are summarized and reported in terms of frequency distribution. The difference in the proportion of pain control within 72 h of admission was compared between matched cohorts (PCA and intermittent) using Chi-square test/Fisher's exact test. Independent sample *t*-test was used to compare the cumulative opioid doses and side effects between matched cohorts (PCA and intermittent groups) accordingly.

Results

We have screened 117 patients during the period from January 2010 to December 2014. Of those, 99 (84.6%) met the study inclusion criteria and 18 patients (15.4%) were excluded from the study. Figure 1 illustrates the patients' enrollment in this study. Males were 47% of the patients and 52% were females with mean age of 26.9 years. Pain score on admission was 5 for both groups as shown in Table 2. Table 3 presents the baseline characteristics for intermittent IV and PCA group.

During the first 72 h of admission, there was a significant reduction in pain score for patients in intermittent IV group compared to those in PCA group ($P < 0.0004$) where the mean pain scores were 3 and 5, respectively. During the 1st day of admission, pain relief was statistically significant in the intermittent IV group compared to PCA group ($P < 0.0004$) where 2.7% of patients had no pain, 24.3% had mild pain, 60.8% had moderate pain, and 12.1% of patients had severe pain. In the PCA group, 84% of patients had scored moderate pain, and 16% of them had scored severe pain.

During the 2nd day of admission, pain relief was statistically significant in the intermittent IV group compared to PCA group ($P < 0.0008$) where, in the intermittent IV group, 8.1% of patients had no pain, 29.7% had mild pain, 59.5% had moderate pain, and 2.7% of patients had severe pain. In the PCA group, 12% had mild pain, 76% had moderate pain, and 12% of patients had severe pain.

On the 3rd day of admission, pain relief was statistically significant in the intermittent IV group compared to PCA group ($P < 0.0032$) where 12.1% of patients had no pain, 22.9% had mild pain, 60.8% had moderate pain, and 4.2% of patients had severe pain. In the PCA group, 4% of patients had no pain, 12% had mild pain, 72% had moderate pain, and 12% of patients had severe pain. The results of pain scores among patients in the two treatment groups over 72 h of admission (3 days) are summarized in Table 4.

Table 1: Opioid equianalgesic dose

Opioid	Equianalgesic dose
Parenteral opioid	
Morphine	10 mg
Hydromorphone	1.5 mg
Fentanyl	0.1 mg
Oral opioid	
Morphine	30 mg
Hydromorphone	7.5 mg
Tylenol #3 (codeine)	120 mg
Percocet (oxycodone)	20 mg

Table 2: Pain scores among the participants on admission

Pain on admission	Mean±SD
Female	5.21
Male	5.68
All	5.43±1.73

SD: Standard deviation

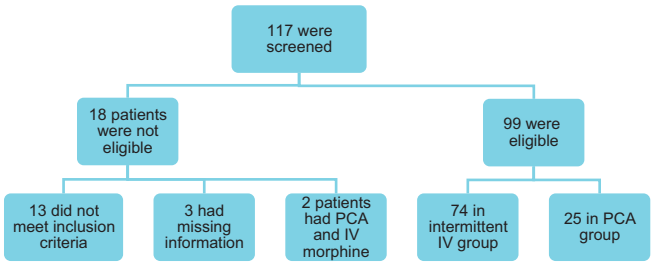

Figure 1: Patients' enrollment in the study

The mean total amount of morphine administered over 72 h of admission was significantly higher ($P < 0.000003$) in PCA group where it was 777 ± 175 mg compared to the intermittent IV group where it was149 ± 74 mg. On the 1st day of admission, the cumulative daily dose of morphine equivalent was significantly higher ($P < 0.00000067$) in PCA group (215 ± 128 mg) compared to the intermittent IV group (44 ± 25 mg). During the 2nd day of admission, the cumulative daily dose of morphine equivalent was significantly higher ($P < 0.00000000050$) in PCA group (331 ± 101 mg) compared to the intermittent IV group (45 ± 28 mg). During the 3rd day of admission, the cumulative daily dose of morphine equivalent was significantly higher ($P < 0.00000000085$) in PCA group (230 ± 84 mg) compared to the intermittent IV group (50 ± 31 mg). These findings are presented in Table 5. No patients in both groups had shown signs of hypotension or respiratory depression over the 72 h of admission.

Table 3: Average baseline characteristics of patients on admission

	Intermittent IV	PCA
Vital signs on admission		
Systole (mm Hg)	114±11	113±17
Diastole (mm Hg)	67±10	64±14
HR (beat/min)	98±17	92±16
RR (breath/min)	20±2	19±2
PO_2 (%)	97±3	98±2
Baseline chemistry and CBC		
Serum (μmol/L)	53±16	44±7
ALT (U/L)	32±40	23±23
AST (U/L)	42±38	34±27
WBC (109/L)	12±12	12±5
Hgb (109/L)	100±17	85±14
Platelet (109/L)	432±286	367±259

IV: Intravenous; PCA: Patient-controlled analgesia; HR: Heart rate; RR: Respiratory rate; CBC: Complete blood count; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; WBC: White blood cell; Hgb: Hemoglobin

Table 4: Pain scores among the patients in the two treatment groups over 3 days

	No pain (%)	Mild pain (%)	Moderate pain (%)	Severe pain (%)	*P*
Day 1					
Intermittent IV	2.7	24	60.8	12.1	0.0004
PCA	0	0	84	16	
Day 2					
Intermittent IV	8.1	29.7	59.4	2.7	0.0008
PCA	0	12	76	12	
Day 3					
Intermittent IV	12.1	22.9	60.8	4.2	0.0032
PCA	4	12	72	12	

IV: Intravenous; PCA: Patient-controlled analgesia

Discussion

VOC is a major cause of morbidity, mortality, and a common reason for ED visits and hospitalization among SCD patients.[7,8] Opioid analgesics are the drug of choice for the treatment of acute pain in VOC patients.[6,9-11] PCA is one of the most common methods for providing continuous infusion of opioids in an inpatient setting. PCA is expected to improve pain control by allowing the patients to have an active role in their pain management. PCA is assumed to be a major advancement in the control of pain such as its successful use in controlling cancer and postoperative pain.[12-14] However, published literature describing the use of PCA in SCD patients is still limited.

Unlike other studies that have shown a significant advantage in the control of pain using PCA as compared with intermittent parenteral administration of opioids, our retrospective observational study showed that during the first 72 h of admission, intermittent IV injection of morphine was more effective than infusion by PCA in pain control. This can be due to the frequent dosing employed in the intermittent IV regimen which was every 30–60 min.

Our data showed that the total amount of morphine administered over 72 h was significantly higher in the PCA group when compared with the intermittent IV group. This is in contrast to the findings of one small trial that found

Table 5: The cumulative opioid daily dose given to the patients in the two treatment groups over 3 days

	Regular morphine	PRN morphine	Other opioid-regular	Other opioid-PRN	Cumulative daily dose	*P*
Daily cumulative opioid doses day 1 (mg)						
Intermittent IV	28±14	12±14	2.5±6	0.72±1	44±25	0.00000067
PCA	205±129	4±6	5±8	0	215±128	
Daily cumulative opioid doses day 2 (mg)						
Intermittent IV	34±12	15±15	4±13	0.72±1	54±28	0.00000000050
PCA	326±101	0	5±10	0	331±101	
Daily cumulative opioid doses day 3 (mg)						
Intermittent IV	29±15	12±11	7±22	0±2	50±31	0.00000000085
PCA	226±96	0	2±7	1±3	230±84	

IV: Intravenous; PCA: Patient-controlled analgesia; PRN: As needed

out that the total amount of morphine administered did not differ significantly ($P = 0.623$) between the intermittent IV group and the PCA group.[16] Our findings can be explained by the tendency of the patients to respond to the immediate availability of morphine when it is offered to them to be received as an on-demand analgesic regimens. A study by Keats[17] has shown that the number of analgesic doses administered was in direct proportion to the availability of nursing staff and not to the degree of pain that was experienced by the patient. In addition, our findings indicated that clinically significant hypotension or respiratory depression was not observed in both groups over the 72 h of admission. This is similar to the results reported by Gonzalez *et al*.[16] where they did not find any significant differences in terms of hypotension and respiratory depression between the PCA and intermittent IV groups.

The limitations to be considered in our study are the relatively small sample size and the nonsignificant results related to the differences between groups which are probably due to a Type II error. In addition, since our approach is a retrospective study, it might be subject to some bias in data selection and analysis. Furthermore, some confounding variables in the study may go unrecognized due to inadequate knowledge of how they can interrelate with the outcome of interest. For such reasons, further larger studies are required to confirm our results.

Conclusion

VOC is a major cause of morbidity, mortality and is also a common reason for ED visits and hospitalization among SCD patients. Our data indicated that during the first 72 h of admission, intermittent IV morphine was more effective than PCA in pain control of SCD patients.

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Conflicts of interest
There are no conflicts of interest.

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