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Clinical Guidelines for Management of Acute Painful Episodes of Vaso-Occlusive Crisis in Children with Sickle Cell Disease

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Abstract

Sickle cell disease (SCD) is an inherited disease resulted due to a single mutation in beta globin gene. It changes normal red blood cells into sickle-shaped cells, just rendering their ability to carry oxygen to tissues and cells. SCD involves many fatal clinical complications including very painful vaso-occlusive crisis (VOC), the later caused by sickled erythrocytes-mediated ischemic tissue injury and obstruction of blood flow that leads. Pain in VOC is caused by hypoxia, acidosis, fever, infections, dehydration, obstructive sleep apnea, abrupt changes in weather (hot / cold), menstruation and pregnancy etc. Pain in VOC is very severe and is associated with many other life-threatening clinical complications. Therefore, it is needed be managed as early as possible, otherwise persistent pain can weaken patients physically and psychologically. There are no specific laboratory indicators for VOC and diagnosis is made on the basis of history and physical examination. We formulated clinical guidelines for the management of acute painful crisis (VOC) in sickle cell patients based upon updated published medical literature, in addition to our experience of treating sickle cell patients King Abdulaziz National Guards Hospital, Al-Ahsa, Saudi Arabia, which is its application to an Asian publication. This report describes details of these clinical guidelines for management of acute painful vaso-occlusive crisis in sickle cell patients.



Introduction

Sickle cell disease (SCD) is an autosomal recessive disorder caused by a single gene mutation that transforms normal red blood cells into sickle-shaped cells [1]. It leads to many fatal clinical complications including vaso-occlusive crisis (VOC) [2]. The sickled erythrocytes cause ischemic tissue injury by obstructing blood flow that leads to VOC [3]. The reduction in blood flow due to sickle-shaped erythrocytes causes hypoxia and acidosis that promotes the process of sickle-cell formation and ischemic tissue injury.

Intensity and duration of VOC varies not only between different patients but even in same patient during different episodes of VOC [4]. Pain in VOC is caused by hypoxia, acidosis, fever, infections, dehydration, obstructive sleep apnea, abrupt changes in weather (hot / cold), menstruation and pregnancy [3]. Abdominal pain and pain in bones like in back, extremities and swelling of finger and toe joints (dactylitis or hand-foot syndrome) are mostly experienced due to VOC [5]. The bone pain is the most common manifestation and may be accompanied by inflammation, redness, warmth and low fever. Bone pain may be symmetrical (affecting the similar joints on left and right side of the body), asymmetrical (pain affecting bone/joint of one side of the body) or migratory (pain spreading from one joint to the other). Dactylitis is more common in SCD patients with age of 3 years and below while older patients present with abdominal and back pain [6]. Although abdominal pain, if present in SCD children, is mild, but it may be accompanied with other manifestations like pelvic inflammatory disease, urinary tract infection, cholecystitis, pancreatitis, appendicitis, splenic sequestration, liver sequestration, pneumonia and chest crisis and it is necessary to rule-out these complications [4]. Moreover, in case of severe painful crisis, patients may experience acute chest syndrome due to sickling in the small blood vessels of the lungs [7, 8]. It may involve the most devastating central nervous system complications including overt stroke in 10% SCD children and silent cerebral infarcts in about 35% SCD patients [9]. CNS manifestations lead to many neuropsychological complications. Therefore, it is necessary to rule out these complications in SCD children presented with painful VOC.

Due to its severity and/or its association with many other serious clinical manifestations, treatment for pain in VOC should started as soon as diagnosis is made, otherwise persistence of pain can weaken patients physically and psychologically [3, 4]. There are no specific laboratory features indicative of VOC and therefore diagnosis is merely made on the basis of history and physical examination [10, 11]. At King Abdulaziz National Guards Hospital Al-Ahsa, we developed some clinical guidelines for the management of acute painful crisis (VOC) in sickle cell patients. These guidelines are based upon our experience of managing VOC in sickle cell patients and other published guidelines from prestigious health centers in North America. Below we are presenting an outline of these guidelines.

Methods

Literature Search and Selection Criteria: We utilized different databases like PubMed (NCBI), Scopus, Google scholar and google to search the articles and published material related to our review paper. Different keywords utilized to search data were "Sickle cell disease, Vaso-Occlusive Crisis, Acute Pain, management and Pediatric". Original peer / reviewed articles, review articles, meta-analysis and clinical trials were considered for this review was addressing clinical management of acute pain in SCD patients with VOC. Case studies were excluded.

Discussion

SCD patient management in ER (Emergency Department) (Grade C) [12]

ER assessment of SCD patients with fever: If SCD patient has consistent fever of 38.5 °C, transfer patient on ER bed and follow "Clinical Guidelines for Fever Management". Carry out a thorough assessment of the patient after administration of antibiotics (Appendix 1).

ER assessment of SCD patients without fever:

Transfer SCD patient without fever to a BED at the earliest. Take brief history and carry out physical examination concurrently with measures as given in Table 1. If child is having fever, respiratory illness or/and fever, go for x-ray of the chest as well as monitor his/her oxygen (O₂) saturation. If patient is complaining of severe respiratory distress, request for arterial blood gas (ABC) level testing additionally [13, 14].

History	Physical examination	Laboratory tests
<ol style="list-style-type: none"> Nature of pain Duration Location Severity of pain (See Pain Assessment Policy) Compare pain with previous episodes of the crisis Analgesics already used Associated symptoms 	<ol style="list-style-type: none"> Check pulse, blood pressure, body temperature, and breathing rate, including oxygen saturation, cardiopulmonary and hydration status. Check size of the spleen Examine patient's neurological system. Check if patient has jaundice. Look for signs of infection. 	<ol style="list-style-type: none"> Request complete blood counts (CBC), differential blood cell counts and reticulocyte count. Go for typing of blood groups and request to crossmatch blood in case if the child is in severe pain or if his/her hemoglobin level is 15 grams per liter or more below the baseline. Moreover, if number of reticulocytes below normal, it is an indication of bone marrow suppression. If there are clinical indications, go for urine analysis and electrolytes. If child is experiencing abdominal pain, go for liver function test and amylase testing.

Table 1: SCD patient management in ER (Emergency Department)

If you find patient febrile (feverish), dehydrated or complaining of moderate to severe pain, insert an intravenous (I.V.) catheter.

Page and inform the Hematology consult service if available. Hematology consultant should examine all SCD patients who are have serious condition and should arrange their proper follow-up. Following are criteria to see if any patient has serious illness:

- Patients in shock (i.e. life-threatening medical condition) with symptoms are very low blood pressure etc.
- Patients with aplastic crisis, acute splenic sequestration crisis, sepsis, meningitis, stroke etc.
- Decompensating patients, for example, patients who progressing into chest crisis etc.
- Patients showing oxygen saturation less than 90% while breathing room air.

In case of fever, acute chest crisis, gallstones etc., please follow other guidelines of "Sickle Cell Management Protocols" specific to these complications [14-16].

Pain management through Medication in Emergency department (ER)

Please adopt protocols provided in table 2 to manage pain, depending upon pain severity [17, 18]:

Adjunct pain relief management: For mild, moderate and severe pain, Acetaminophen 75 mg/kg/day PO (maximum dose 4g/day) and an non-steroidal anti-inflammatory drug (NSAID) can be given as adjunct pain relief medication along with morphine, unless there are any contraindications to their use. Before using NSAIDs, assess renal function and consult with pharmacist if you find results abnormal [17].

Recommended NSAIDs include:

Ibuprofen: For children 6 months-12 years old: 5-10 mg/kg/dose PO q6-8h (orally, every 6-8 hours); Not to exceed 40 mg/kg/day or 2400 mg/day.

Naproxen: 10-20 mg/kg/day PO divided BID (orally, twice daily); Not to exceed 1 g/day).

Ketorolac: 0.5 mg/kg/dose intravenous (I.V.) q6-8h (every 6-8 hours); Not to exceed 15 mg/dose), maximum for 48 hours and after that change switch to ibuprofen or naproxen.

Pain management for Indoor patients [18-20]:

You need to admit patient if pain is inadequately controlled with oral analgesics or in case of other complications such as fever, dehydration etc.

Patients should be admitted to hospital ward only under General Pediatrics Service.

Pain management through Medication for outdoor patients [18, 19]

- Prescribe oral morphine dose that adequately relieved pain as stated in 2.1.7 (don't exceed 15 mg/dose). In case patient needed higher doses during previous ER visits for painful VOC,

consult patient chart and hematology service. Reevaluate the patient if in not relieved in 48 hours.

Pain Severity	Pain medication	Comments
Mild to moderate pain	<p>Morphine: 0.3-0.5 mg/kg/dose PO (by mouth) q4h (every four hours) PRN (as needed). The maximum dose is 15 mg/dose. OR Hydromorphone: 0.04-0.08 mg/kg/dose PO q4h PRN. Do not exceed 4mg/dose.</p>	<p>Induce patients to drink water. In case pain is not relieved adequately in half to one hour, switch to guidelines for moderate to severe pain provided below. In case of adequate pain relief and if there are no other acute complications, you may discharge the patients and prescribe oral analgesics. Please consult guidelines for "Outpatient Management" for this purpose.</p>
Moderate to severe pain	<p>Morphine: Intravenous (I.V.) bolus of 0.05- 0.1 mg/kg/dose OR Hydromorphone: I.V. bolus of 0.015-0.02 mg/kg/dose (max dose 1 mg) or PO bolus of 0.04-0.08 mg/kg/dose (max dose: 4 mg)</p>	<p>You may consider giving intravenous bolus again after one hour or later in case if pain is not relieved adequately. In case a patient needs more than 2 intermittent I.V. doses of opioid, he/she must be admitted (please consult guidelines for inpatient management) and an opioid infusion should be given for severe pain (as stated below). In case if pain is relieved adequately for two hours with 1-2 doses of intermittent intravenous opioid, you need to change to equivalent oral opioid dose. You may discharge the patient provided pain is controlled on oral opioid and patient is tolerating oral fluids. Please give intravenous fluids to all patients with moderate to severe pain. It should consist of a 10mL/kg bolus of saline, followed by 1.5 times the maintenance intravenous dose of 5% dextrose in 0.9% sodium chloride solution.</p>
Severe Pain	<p>Morphine: I.V. bolus of 0.05-0.1 mg/kg/dose (do not exceed 7.5 mg/dose) followed by morphine continuous I.V. infusion 40 micrograms /kg /hour. Additionally, patient can be given boluses of morphine (0.05 mg/kg) q1-2h (every 1-2 hours) PRN for breakthrough pain (sudden and brief flare-up of pain). OR Hydromorphone: I.V. bolus of 0.015-0.02mg/kg/dose (don't exceed 1 mg/dose) followed by Hydromorphone continuous I.V. infusion. Additionally, patient can be given boluses of hydromorphone 0.015 mg/kg (8 micrograms/kg/hour) q1-2h PRN for breakthrough pain</p>	<p>To all patients in moderate to severe pain, administer fluids intravenously, as: First give a bolus of saline (10 milliliter per kilogram of body weight), after that administer 1.5 times of the maintenance I.V. rate, with dextrose 5% in sodium chloride 0.9% solution.</p>

Table 2: Pain management through Medication in Emergency department [18].



- For mild, moderate and severe pain, Acetaminophen 75 mg/kg/day PO (maximum dose 4g/day) AND a non-steroidal anti-inflammatory drug (NSAID) can be given as adjunct pain relief medication along with morphine, unless there are any contraindications to their use. Please consult **table 3** for dosing.

Patients are needed to be observed closely for signs of deterioration and are required to be monitored continuously with cardiac and oxygen (O₂) saturation, for vital signs every four hours, for fluid input and output as well as daily weight. It is required to carry out assessment of patient's comfort level every 4 hours. This assessment is also required before as well as after every treatment provided for pain management and even after any non-pharmacological management of with pain.

Pain medication	Recommended Dose	Comments
Morphine	0.3-0.5 mg/kg/dose PO (by mouth) Q4H (every 4 hours) PRN (as needed). Don't exceed 15 mg/dose.	In case patient needed higher doses during previous ER visits for painful VOC, consult patient chart and hematology service. Reevaluate the patient if in not relieved in 48 hours.
Acetaminophen AND a non-steroidal anti-inflammatory drug (NSAID) as adjunct pain relief medication along with morphine, unless there are any contraindications to their use Following NSAIDs are recommended:	75 mg/kg/day PO Maximum dose: 4 g/day	Before using NSAIDs, assess renal function and consult with pharmacist if you find results abnormal
Ibuprofen	For patients aged 6 months to 12 years: 5-10 mg/kg/dose PO q6-8h (by mouth, every 6-8 hours) Don't exceed 40 mg/kg/day or 2400 mg/day	None
Naproxen	10-20 mg/kg/day PO divided bid (orally, twice daily) Don't exceed 1 g/day.	None
Ketorolac	0.5 mg/kg/dose intravenous q6-8h (every 6-8 hours). Don't exceed 15 mg/dose. Use it for 48 hours and change to ibuprofen or naproxen.	None

Table 3: Drug dosing for pain management (outdoor patients).

If patient is hospitalized with chest and back pain, refer to him/her to Physiotherapy. It is recommended for physiotherapist to determine if incentive spirometry (10 breaths every 1-2 hours while awake) is appropriate for older children (8 years or older). For younger children, physiotherapist should motivate them use bubbles for deep breathing. The physiotherapist should also encourage walking without any support (ambulation) and

any other activities keeping in consideration patient's tolerance. Per recommendations of physiotherapists, other health professionals involved should also promote child's mobility [13].

Referral of the patient to Physiotherapy is required if he/she is showing significant decrease in mobility or restricted joint movement.

To improve patient comfort level, non-pharmacological interventions such as massage, heating pads, warm baths, and other such methods should be utilized. It is advisable for "Child Life representative" to recommend structured daily activity for the patient. Use of Imagery and distraction prove to be helpful.

In case if pain is not relieved even after using analgesics or if any pain-related are encountered, consultation with Pain Management Team is highly recommended.

Give patient boluses of morphine intravenously for breakthrough pain (consult table 4 for exact doses). After maintaining effective dose for 24 hours, gradually decrease dose by up to 20 micrograms/kg/hour in next 24 hours. If patient is stable, continuous intravenous morphine may be replaced by an equal dose of long-acting oral morphine (consult table 4 for exact doses).

Step-down therapy: For those patients who are comfortable, it is recommended to change to oral analgesics (morphine 0.3-0.5 mg/kg/dose orally every 4 hours as needed (PO, q4h, PRN prn). Don't exceed 15 mg/dose (consult table 4 for exact doses).

For mild, moderate and severe pain, Acetaminophen 75 mg/kg/day PO (maximum dose 4g/day) AND a non-steroidal anti-inflammatory drug (NSAID) can be given as adjunct pain relief medication along with morphine, unless there are any contraindications to their use (consult table 4 for exact doses).

In case of pain persisting for more than 24-48 hours in patients older than 6 years of age, using Patient Controlled Analgesia (PCA) pump is recommended [21-23]. Similarly, utilize a PCA pump for any child already treated with a PCA pump or for children who did not achieve adequate analgesia. A PCA pump has capability to deliver a continuous infusion as well as intravenous boluses of morphine or any other medication per patient need and a required dose and interval of medication can be pre-programmed by the prescriber (physician) and therefore chances of overdosing are negligible if PCA pump is used. Please contact (through pager) the Pain Management Team to get PCA pump and they can set it at its basal rate, bolus rate, and lockout time. It is mandatory to observe patients carefully for opioid toxicity when patients are on morphine. The indications of opioid toxicity include hypotension, bradycardia, drowsiness, coma, pinpoint pupils, cold clammy skin, and hypoventilation. It is required to regularly monitor and record patient's heart rate, respiratory rate and oxygen saturation while observing patient for opioid toxicity.

Use of stool softeners: If the patient does not have diarrhea, it is required to administer him/her a stool softener such as Docusate Sodium (5 mg/kg/day for

children). You administer it in three equal doses or as a single daily dose. Adult daily dose is 100-200 mg.

Name of drug	Drug Dose	Comments
Oral Morphine	0.3-0.5 mg/kg/dose PO q4h PRN (orally, every 4 hours, as needed). Don't exceed 15 mg/dose.	If patient is stable, continuous intravenous morphine may be replaced by an equal dose of long-acting oral morphine
Morphine continuous intravenous (I.V.) infusion	40 micrograms /kg/hour.	<ul style="list-style-type: none"> Intravenous morphine (40 micrograms /kg/hour) should be continued. In case if pain is not relieved adequately, adjust the dose every 8 hours (q8h) by increasing 10-20 micrograms/kg/hour. Don't exceed the dose of 100 micrograms/kg/hour. In case of breakthrough pain, it is permissible to give boluses of 0.05 mg/kg morphine every 1-2 hours intravenously as needed (q1-2h, IV PRN). After maintaining effective dose for 24 hours, gradually decrease dose by up to 20 micrograms/kg/hour in next 24 hours.
Acetaminophen AND NSAIDs	75 mg/kg/day PO Maximum dose: 4 g/day	-
Along with Acetaminophen, non-steroidal anti-inflammatory drugs ((NSAIDs) as adjunct pain relief medication along with morphine, unless there are any contraindications to their use.		
Following NSAIDs are recommended:		Before using NSAIDs, assess renal function and consult with pharmacist if you find results abnormal
Ibuprofen	For patients aged 6 months to 12 years: 5-10 mg/kg/dose PO q6-8h (by mouth, every 6-8 hours) Don't exceed 40 mg/kg/day or 2400 mg/day	None
Naproxen	10-20 mg/kg/day PO divided bid (orally, twice daily) Don't exceed 1 g/day.	None
Ketorolac	0.5 mg/kg/dose intravenous q6-8h (every 6-8 hours). Don't exceed 15 mg/dose. Use it for 48 hours and change to ibuprofen or naproxen.	None

Table 4: Pain management through Medication for indoor patients

Use of antihistamines: For patients with pruritus, prescribe antihistamines PRN (as needed).

Hydration: For hydrating patients, fluids should be continually given intravenously or orally at 1-1.5 times the maintenance rate. Fluid maintenance rate can be calculated using specific charts and formulas provided in medical literature [24, 25].

Oxygen: Systematic use of oxygen is not recommended for VOC in sickle cell patients, based upon many studies and reports. Nevertheless, SCD children with VOC may develop hypoxia that can promote sickling process. Accordingly, it is highly recommended to regularly monitor oxygen saturation in such patients and if patients have indications of hypoxemia, oxygen should be provided [26, 27].

Use of Corticosteroids: For sickle cell patients, effectiveness of corticosteroids as an adjunct therapy for reducing pain duration is not clear. Therefore, it is recommended to avoid using corticosteroids routinely unless data from some new clinical trials supports their use [27].

Guidelines for discharge patients:
The patients can be discharged in following cases:

- If patients are tolerating fluids and medications orally.
- If there is adequate pain relief using oral medications.
- If all concurrent problems of the patient are resolved.

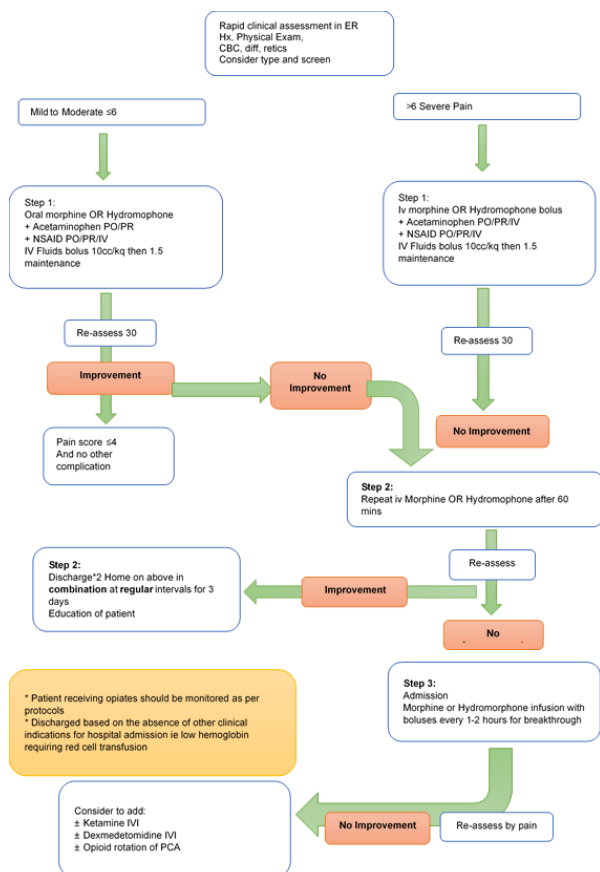
Drug	Route	Dose	Frequency (Hours)
Morphine	Oral	0.3-0.5mg/kg/dose	4h (max 15mg/dose)
	IV bolus	0.1 mg/kg/dose	Max 7.5 mg /dose
	Continues IV infusion	40 mcg/kg/h	NA
	IV Breakthrough	0.05 mg/kg	Q1-2 PRN
Hydromorphone	oral	0.04-0.08 mg/kg/dose	Q4h PRN max 4mg/dose
	IV bolus	0.015-0.02mg/kg/dose	Max 1mg/dose
	Continues IV infusion	8mcg/kg/h	NA
	IV breakthrough	0.015 mg/kg	1-2 PRN
ACETAMINOPHEN	Oral	75mg/kg/day	Max 4gm /day
IBUPROFEN	Oral	5-10 mg/kg/dose	6-8 (max 40mg/kg/day)
Naproxen	Oral	5-10 mg/kg	Q 12 (max 1 gm /day)
Ketorolac		0.5mg/kg/dose	Q 6-8 (max 15mg/dose)x48 hours max

Table 5: List of drugs for pain management in sickle cell patients with route of administration and dosage.

Conclusion

Sickle cell disease (SCD) is a familial disorder resulted due to a single mutation in beta globin gene. It leads to many fatal clinical complications including painful vaso-occlusive crisis (VOC), requiring acute clinical management. VOC pain is caused by hypoxia, acidosis, fever, infections, dehydration, obstructive sleep apnea, abrupt changes in weather (hot / cold), menstruation and pregnancy etc. Pain in VOC is very severe and leads to many other life-threatening clinical complications if not timely diagnosed and properly treated. Nevertheless, there are clear laboratory indicators for VOC. We formulated clinical guidelines for the management of acute painful crisis (VOC) in sickle cell patients by

utilizing published clinical data as well as our experience of treating sickle cell patients at a tertiary care hospital in Al-Ahsa, Saudi Arabia, as it fits Asian populations better. This article describes details of these clinical guidelines for management of acute painful vaso-occlusive crisis in sickle cell patients. It details practical clinical measures to be taken by medical specialists in different fields of medicine and their associated healthcare staff to treat painful VOC in sickle cell patients.



Pain Pathway for Sickle Cell Disease in Children (Appendix 1)

Important notes:

1. Please consider allergies, drug effects, side effects and contra-indications prior to administration.
2. Patients on regular opiates should receive stool softeners.

Competing Interests

None.

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