Perioperative considerations for patients with sickle cell disease: a narrative review

Considérations périopératoires pour les patients atteints d'anémie falciforme : un compte rendu narratif

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Abstract

Purpose Approximately 200,000 individuals worldwide are born annually with sickle cell disease (SCD). Regions with the highest rates of SCD include Africa, the Mediterranean, and Asia, where its prevalence is estimated to be 2–6% of the population. An estimated 70,000–100,000 people in the United States have SCD. Due to enhanced newborn screening, a better understanding of this disease, and more aggressive therapy, many sickle cell patients survive into their adult years and present more frequently for surgery.

Source The authors identified relevant medical literature by searching PubMed, MEDLINE®, EMBASE™, Scopus™, Web of Science, and Google Scholar databases for English language publications appearing from 1972–September 2016. Case reports, abstracts, review articles, and original research articles were reviewed—with particular focus on the pathophysiology and medical management of SCD and any anesthesia-related issues.

Principal findings Perioperative physicians should be familiar with the triggers of a sickle cell crisis and vaso-occlusive disease. Sickle cell disease affects various organ systems, including the central nervous, cardiovascular, pulmonary, genitourinary, and musculoskeletal systems. Preoperative assessment should focus on end-organ dysfunction. Controversy continues regarding if and when sickle cell patients should receive transfusions and which anesthetic technique (regional or general) confers any benefits. Timely, appropriate, and sufficient analgesia is

critical, especially when patients experience a vaso-occlusive crisis, acute chest syndrome, or acute postoperative pain.

Conclusion Effective management of SCD patients in the perioperative setting requires familiarity with the epidemiology, pathophysiology, clinical manifestations, and treatment of SCD.

Résumé

Objectif Chaque année, quelques 200 000 personnes atteintes d'anémie falciforme naissent dans le monde. Les régions affichant les taux les plus élevés de cette maladie sont l'Afrique, le bassin méditerranéen et l'Asie, où sa prévalence est estimée à 2–6 % de la population. Aux États-Unis, on estime que 70 000–100 000 personnes sont atteintes d'anémie falciforme. Grâce à un meilleur dépistage des nouveau-nés, une meilleure compréhension de la maladie et un traitement plus vigoureux, bon nombre de patients affectés par la maladie survivent jusqu'à l'âge adulte et se présentent donc plus fréquemment pour subir une chirurgie.

Source Les auteurs ont identifié la littérature pertinente en réalisant des recherches dans les bases de données PubMed, MEDLINE®, EMBASE™, Scopus™, Web of Science et Google Scholar, afin d'en extraire les publications de langue anglaise apparaissant entre 1972 et septembre 2016. Les présentations de cas, résumés, articles de synthèse et articles de recherches originales ont été passés en revue – en portant une attention particulière à la physiopathologie et à la prise en charge médicale de l'anémie falciforme, ainsi qu'à toutes les questions liées à l'anesthésie.

Constatations principales Les médecins périopératoires devraient bien connaître les éléments déclencheurs d'une

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crise d'anémie falciforme et de crise vaso-occlusive. L'anémie falciforme touche plusieurs systèmes d'organes, notamment les systèmes nerveux central, cardiovasculaire, pulmonaire, génito-urinaire et musculo-squelettique. L'évaluation préopératoire doit se concentrer sur les dysfonctionnements des organes cibles. La controverse continue quant à déterminer si et quand les patients atteints d'anémie falciforme devraient recevoir des transfusions et quelle technique anesthésique (régionale ou générale) confère des bienfaits. Une analgésie opportune, adaptée et suffisante est essentielle, particulièrement lorsque les patients subissent une crise vaso-occlusive, un syndrome thoracique aigu ou souffrent de douleurs postopératoires aiguës.

Conclusion Une prise en charge efficace des patients atteints d'anémie falciforme en période périopératoire nécessite une bonne connaissance de l'épidémiologie, de la physiopathologie, des manifestations cliniques et du traitement de l'anémie falciforme.

In 1910, James B. Herrick reported a novel case of sickle cell disease (SCD) in the medical literature, describing a patient who presented with jaundice, shortness of breath, lymphadenopathy, dark urine, leg ulcers, epigastric pain, and anemia. Upon further examination, the red blood cells (RBCs) of this patient appeared to be elongated and sickle-shaped when observed under the microscope (Figure).^{1,2} Sickle cell disease is the most common inherited disorder of RBCs and is thought to have evolved because it confers a protective effect against malaria infection.³ There are several genotypes for SCD, including HgbSS and HgbS β^0 -thalassemia, all of which are referred to as sickle cell anemia.² Due to early neonatal screening and improved

prevention and treatment of a sickle cell crisis, patients are surviving and thriving into their adult years when chronic organ dysfunction manifests.^{4,5} This increases the likelihood of seeing a sickle cell patient in the perioperative period.

The clinical manifestations of SCD are myriad and multisystemic, but the underlying pathophysiologic event is the sickling of RBCs (secondary to stresses such as hypoxia, acidosis, or hypothermia), leading to vascular occlusion and end-organ ischemia or infarction (Table 1). Patients with sickle cell disease pose unique challenges due to the chronic manifestations of their disease and their specific vulnerabilities to the physiologic stresses of surgery and anesthesia. As perioperative physicians, anesthesiologists require an understanding of the epidemiology, pathophysiology, and clinical manifestations of SCD, as well as the current management goals/treatments for safe and optimal care for these patients.

To identify relevant medical literature for this review, the authors searched the PubMed, MEDLINE®, EMBASE™, Scopus™, Web of Science, and Google Scholar databases for English language publications covering a 44-year period from 1972–September 2016. Search terms and phrases included sickle cell disease, anesthesia, pediatric sickle cell disease, adult sickle cell disease, transfusion in sickle cell disease, analgesia in sickle cell disease, and sickle cell disease and pregnancy. Case reports, abstracts, review articles, and original research articles were reviewed—with particular focus on the pathophysiology and medical management of SCD and anesthesia-related issues. In fact, there is a paucity of comprehensive literature suitable for the perioperative physician, and we have attempted to assimilate the relevant information.

Figure Electron micrograph of sickled red blood cells

Table 1 Signs and symptoms of SCD based on involved organ systems

Organ System	Signs and Symptoms
Hematologic	Megaloblastic anemia, aplastic anemia, splenic infarction, and splenic sequestration
Musculoskeletal	Dactylitis, bone marrow infarcts, osteomyelitis, growth impairment, painful crisis
Cardiovascular	Cardiomegaly, systolic ejection murmurs, congestive heart failure, cor pulmonale, acute chest syndrome
Central nervous	Stroke: -hemorrhagic: pediatrics -ischemic: adults Cranial neuropathies
Genitourinary	Renal infarction, hematuria, renal failure, priapism
Pulmonary	Pulmonary fibrosis, pulmonary infarction, pulmonary embolism, cor pulmonale, high alveolar-to-arterial gradient, obstructive lung disease (pediatrics), restrictive lung disease (adults)

SCD = sickle cell disease

Epidemiology

Individuals most commonly afflicted with SCD are of African, Mediterranean, and Asian descent. About 2–6% of the population is affected in these regions, while even higher rates (> 6%) are estimated in sub-Saharan Africa, the Persian Gulf, and the Indian subcontinent.^{6,7} An estimated 70,000–100,000 individuals in the USA have SCD, while an additional 3.5 million individuals in the USA are heterozygous carriers of HgbS (HgbAS genotype)—i.e., they have sickle cell trait.² While the vast majority of these patients are born in sub-Saharan Africa, clinicians in North America regularly encounter patients with SCD. Roughly 2,000 newborns are afflicted with this condition annually in the USA.^{6,7} Reports on the prevalence of SCD in the Canadian population are very limited; however, due to demographic and genotype distribution, the incidence of SCD in Canada is likely similar to rates seen in the USA.⁸ Several newborn screening programs across Canada help to gauge the prevalence of SCD and enable early and targeted therapy to those afflicted individuals.^{8,9} In developing nations, > 50% of children with SCD die before reaching five years of age.^{10–13} In contrast, the mean life expectancy in developed countries is 39 years of age, largely because of universal newborn screening, the use of prophylactic penicillin, and the pneumococcal vaccine.^{10–12}

Pathophysiology

Hemoglobin exists in a variety of forms. Most prevalent is hemoglobin A (96–98%), which is comprised of two α and two β globin chains. Hemoglobin A2 (1.5–3.2%) is comprised of two α and two δ globin chains. Fetal hemoglobin (0.5–0.8%) consists of two α and two γ globin chains and is the dominant hemoglobin (90%) in the first ten weeks of life.^{4,14} Sickle cell disease is transmitted in

the autosomal recessive fashion.¹⁵ The genetic abnormality responsible for SCD is a point mutation on chromosome 11, leading to an abnormal β -globin subunit of the hemoglobin molecule.^{2,12,16} At low oxygen tension, this altered hemoglobin molecule forms insoluble globulin polymers, causing RBCs to adhere to each other. Vascular endothelial damage and a subsequent inflammatory response ensue, leading to further sickling and ultimately sludging of blood and vascular occlusion.¹⁷ Individuals who are homozygous (HgbSS) have 70–98% of their hemoglobin in HgbSS form and exhibit disease phenotype. Heterozygous individuals (HgbAS) are “carriers”, and an estimated 40% of their hemoglobin is HgbS. These individuals typically do not demonstrate clinical disease.¹⁶ Normal RBC lifespan is 120 days. Sickled RBCs have a lifespan of 10–20 days, are exquisitely fragile, and succumb to the common triggers of sickling, including hypothermia, dehydration, acidosis, and physiologic stress. The ensuing vascular occlusion underlies all the clinical sequelae of SCD and most commonly presents acutely as painful vaso-occlusive crisis (VOC) in the affected part of the body. There are other unique clinical manifestations of the disease which are reviewed below.¹⁸ During an acute pain crisis, HgbS polymerizes, leading to RBC sickling. The sickled RBCs adhere to the vascular endothelium, which further promotes fibrin deposition and occlusion.¹⁹

Chronic medical management

Hydroxyurea is the only medication approved by the United States Food and Drug Administration for treatment of SCD.²⁰ As a disease-modifying drug, hydroxyurea has several functions, including stimulation of HgbF formation, release of endogenous nitric oxide, a decrease in the production of leukocytes and reticulocytes, and a reduction

in the overall incidence of VOC and acute chest syndrome (ACS).^{12,20,21} There is strong evidence to suggest that chronic hydroxyurea therapy lowers mortality.^{22–24} Symptomatic treatment for VOC includes rehydration, supplemental oxygen therapy, aggressive analgesia, and incentive spirometry.⁵ Acute chest syndrome is treated similarly to VOC, with the addition of blood exchange transfusion.⁵ Hematopoietic stem cell transplantation can be an option in patients younger than 16 years of age who have experienced serious complications of SCD, such as stroke, ACS, or refractory pain.^{15,25}

Clinical manifestations and preoperative considerations

The entire body can be affected by sickled RBCs, resulting in a multitude of signs and symptoms (Table 1). Cardiovascular signs include left ventricular hypertrophy, cardiomegaly, and hypertrophic cardiomyopathy due to the anemia-induced chronic high cardiac output. A dilated cardiomyopathy can result from iron overload—a potential complication of transfusion programs. In addition, SCD patients can have systolic ejection murmurs, congestive heart failure, and cor pulmonale from recurrent pulmonary embolism.^{4,26–28} Hypotension can be secondary to chronic anemia, while hypertension may arise from renal failure. In addition to careful assessment of the patient's functional status and electrocardiogram, echocardiography may be useful to assess cardiac function.

Pulmonary manifestations can range from benign to severe, including pulmonary fibrosis, pulmonary hypertension, and ACS.^{28,29} Patients can present with high alveolar-to-arterial oxygen gradients, and up to 53% of patients have signs of asthma. A predominance of obstructive lung disease in children progresses to a more restrictive pattern in adults.^{4,30} Chest radiography, pulse oximetry, and pulmonary function tests may help delineate the degree of pulmonary pathology.

Acute chest syndrome results from vaso-occlusion of the pulmonary vasculature and is a medical emergency—with an associated 10% mortality.³¹ Signs and symptoms include lower chest pain, pleuritis, fever, cough, hypoxia, and pulmonary hypertension. Chest *x-rays* often reveal basilar infiltrates – similar to pneumonia. Children typically present with fever and cough but rarely have pain, while adults typically present with shortness of breath, chills, severe pain, and no fever.^{15,16,31} Treatment of ACS includes supplemental oxygen, incentive spirometry, continuous positive airway pressure, bi-level positive airway pressure, mechanical ventilation, exchange transfusion to reduce HgbS < 30%, antibiotics, bronchodilators, and inhaled nitric oxide. Inhaled nitric oxide helps to dilate the pulmonary vasculature and

decrease right ventricular afterload, thereby improving a V/Q mismatch.^{15,31}

Stroke and cranial nerve neuropathies are commonly seen in SCD. About 17% of pediatric patients will present with brain magnetic resonance imaging (MRI) abnormalities. By 20 years of age, roughly 11% of children with SCD can present with overt stroke symptoms,³² while an estimated 30% of children will present with silent infarcts by the same age.³³ Symptoms of silent infarcts typically last less than 24 hr but contribute to ongoing cognitive impairment, poor academic performance, and subsequent infarcts. Adults typically show intracerebral hemorrhage on MRI.³⁴ Routine monitoring with transcranial Doppler is recommended for patients from two to 16 years of age.³⁵ Psychiatric issues, seizures, poor academic performance, and developmental delay may be indicative of neurovascular disease, including silent infarcts and stroke.^{4,16}

The genitourinary system can also be affected by SCD. Renal symptoms result from infarction of the renal medulla, leading to papillary necrosis, proteinuria, hematuria, and potentially renal failure. Urine protein and creatinine levels are useful in assessing renal function. Persistent priapism can become a urologic emergency requiring urgent intervention to drain stagnated blood from the corpora cavernosa.^{4,5,36,37}

Hemolysis can lead to megaloblastic or aplastic anemia along with liver dysfunction. Chronic hemolysis leads to patients adapting to anemic levels of hemoglobin. These patients have a new “normal” hemoglobin level 6–9 g·dL^{−1}. Folic acid may be administered to prevent megaloblastic anemia. Acute aplastic anemia is characterized by a drop in hemoglobin of 1 g·dL^{−1}·day^{−1}.⁴ These patients are often predisposed to cholelithiasis.^{37,38} Splenic sequestration can result in profound anemia, one of the leading causes of morbidity and mortality in pediatric patients requiring immediate intervention.^{28,39} Chronic hypersplenism is associated with a new “normal” hemoglobin of about 3–4 g·dL^{−1}, with an average RBC lifespan of two–four days.⁴ For children younger than two years of age, elective splenectomy is recommended for one major or two minor sequestration crises.⁴⁰ Auto-infarction of the spleen can lead to more frequent and severe bacterial infections.⁴¹ Infection is quite common and mainly due to streptococcus pneumonia, salmonella, *E. Coli*, parvovirus B19, and Epstein-Barr virus.⁴² Use of the pneumococcal vaccine is critical if the spleen is affected.

With regard to the musculoskeletal system, sickle cell patients can exhibit a painful crisis (with or without fever), dactylitis, bone marrow infarcts, osteomyelitis (due to salmonella), and avascular necrosis.^{4–6,12,37} Typical instigators of sickling and pain crisis include acidosis,

hypotension, hypoxia, infection, low body temperature, stress, vasoconstriction, and venous stasis.²⁵ Pain is one of the most common symptoms of SCD patients admitted to the hospital. Typically, the onset is acute without much warning and can last from days to weeks, affecting the chest, back, abdomen, and extremities. Pain crisis is more frequent at night due to dehydration and nocturnal desaturation. Treatment targets crisis prevention and relief of symptoms with rest, warmth, multimodal analgesia, fluids, and antibiotics.⁴

While there is overlap, clinical manifestations vary substantially from pediatric patients to adult patients (Table 2). Children most often show signs of growth impairment, dactylitis, anemia, sepsis, jaundice, splenomegaly, stroke, pain, and ACS.^{4,31,43} Adults with SCD often present with infection, ACS, pulmonary embolism, liver failure, stroke (hemorrhagic in younger patients and ischemic in patients older than 35 years of age), and heart failure.^{33,39}

Transfusions

The goals of transfusion therapy include decreasing the HgbS to < 30%, minimizing splenic sequestration, treating severe anemia, and avoiding ACS due to low PaO₂.⁴⁴ Exchange transfusions serve to lower the concentration of HgbS, while “top-up” transfusions serve to correct anemia.^{2,44} Chronic transfusion programs exist for primary and secondary stroke prevention.^{5,15,16} Other indications for blood transfusions include acute anemia and ACS. The risks of transfusions include infection, alloimmunization, delayed hemolytic transfusion reaction, an increase in blood viscosity, and iron overload.^{15,16,44,45}

Several trials, including SIT (Silent Cerebral Infarct Multi-Centre Clinical Trial), STOP (Stroke Prevention

Trial in Sickle Cell Anemia), TWiTCH (Transcranial Doppler with Transfusions Changing to Hydroxyurea), and SWiTCH (Stroke With Transfusions Changing to Hydroxyurea), have been conducted to determine whether transitioning to hydroxyurea therapy is as efficacious as chronic transfusion programs to prevent serious complications such as stroke, VOC, and ACS.^{15,18,46} Despite the disease-modifying properties of hydroxyurea, it seems that only regular transfusion therapy is associated with a lower incidence of silent infarcts, stroke, and other serious complications.^{15,47}

Preoperative transfusion has been investigated with randomized-controlled trials,^{38,44,45,48} but these are somewhat limited due to insufficient recruitment of patients and logistical issues regarding prospective follow-up.⁴⁴ One retrospective analysis of SCD pediatric surgical patients suggests that routine preoperative blood transfusion may be unnecessary, especially for minor procedures such as herniorrhaphy, dental/oral surgery, ophthalmological surgery, and tympanostomy tubes.⁴⁵ Nevertheless, in adult surgical patients undergoing low- to medium-risk procedures, a lower rate of complications such as ACS and VOC was observed in patients who were given preoperative transfusions.⁴⁴

Regional vs general anesthesia

Controversy exists regarding the benefits of neuraxial anesthesia (subarachnoid block or epidural) vs general anesthesia for sickle cell patients presenting for surgery (Table 3). Pain is the most common complaint secondary to VOC. Therefore, an anesthetic plan that can prevent and alleviate vaso-occlusive episodes is recommended.²⁵ Neuraxial anesthesia has been advocated in SCD patients because of its associated sympathectomy and vasodilation,

Table 2 Complications of sickle cell disease in pediatric and adult population

Pediatrics	Overlap Pediatrics → Adults	Adults
Delayed growth	Chronic hemolytic anemia	Cardiomegaly
Aplastic crisis	Stroke	Heart failure
Acute splenic sequestration	Immunosuppression	Premature CAD
Autoinfarction	Jaundice	Pulmonary hypertension
Impaired immunity	Vaso-occlusive crisis	Chronic lung disease
Dactylitis	Acute chest syndrome	Liver failure
Left ventricular hypertrophy	Avascular necrosis	Renal failure
Cardiomyopathy	Chronic lower extremity ulcers	Frequent UTIs
Asthma	Priapism	Bone necrosis/loss of bone density
Renal impairment		
Enuresis		

CAD = coronary artery disease; UTIs = urinary tract infections

Table 3 General vs neuraxial/regional anesthesia considerations

Anesthesia type	Advantages	Disadvantages
General	Less frequent hypotension Less anxiety Improved oxygenation with controlled ventilation	Inadequate analgesia Greater blood loss Oversedation → hypoventilation
Neuraxial/regional	Superior analgesia Sympathectomy and vasodilation → fewer vaso-occlusive episodes	Hypotension Bradycardia Postdural puncture headache Increased anxiety with awake patient

thereby decreasing the likelihood of a perioperative vaso-occlusive episode⁴⁹ in addition to providing superior analgesia. Nevertheless, complications such as hypotension, bradycardia, and postdural puncture headaches may pose particular concerns in SCD patients.⁴⁹ Hypotension and bradycardia can precipitate VOC due to increased sickling of RBCs from a low-flow state. Treatment of low blood pressure with vasoconstrictors is controversial because of the potential to reduce blood flow in at-risk vascular beds.^{50,51} In SCD parturients, however, evidence suggests that it is safe to use ephedrine to treat neuraxial-associated hypotension.^{49,52} In order to avoid precipitating a sickling event, it is prudent to treat hypotension expeditiously with intravenous fluids and vasopressors as appropriate.

Untreated anxiety is an important concern with awake patients undergoing surgery as this can precipitate sickling. For this reason, general anesthesia may be advantageous.²⁵ Other benefits of general anesthesia may include less frequent and less severe episodes of hypotension, particularly when anesthesia is induced with careful titration of induction medications.⁵³ Furthermore, use of controlled ventilation facilitates improved oxygenation, which in turn may help prevent postoperative VOC.⁵³ Disadvantages of general anesthesia include the potential for inadequate postoperative analgesia and hypoventilation secondary to the respiratory depressant effects of anesthetic drugs (Table 3). Studies suggest that neuraxial anesthesia may confer benefit in surgical patients with regard to blood loss compared with general anesthesia, and so it is anticipated that this may be of particular relevance to the SCD patient.^{16,49}

Regardless of the anesthetic strategy, it is essential to ensure optimal oxygenation, hydration, perfusion, thermoregulation, sedation, antibiotic prophylaxis, and analgesia, while also considering the need for blood transfusions. Employing this strategy preoperatively and maintaining it intraoperatively and postoperatively is critical to managing this unique patient population.^{16,25}

Analgesia in SCD

When treating perioperative pain in the SCD patient, it is important to distinguish between acute postoperative pain, pain from a VOC, and chronic pain conditions that are common in this population (i.e., leg ulcers, avascular necrosis). Sickle cell pain is worse than postoperative pain and can be as intense as terminal cancer pain.⁵⁴ Different types of pain may respond to different approaches and drugs. General principles include prevention of VOC (hydration, oxygenation, temperature regulation) as well as appropriate use of regional anesthesia and multimodal analgesia. Importantly, though effective for its anti-inflammatory effects, local application of ice to surgical sites should be strictly avoided in this population.

Opioids remain a mainstay for treatment of VOC pain and should be considered as a first-line agent for postoperative pain in patients with SCD.^{16,54} The advantages of opioid therapy include the varied delivery routes, the number of available agents, and the centrally acting mechanism of action which facilitates better drug titration.⁵⁴ Opioid tolerance is very common in patients with SCD due to the chronic nature of sickle cell pain.¹⁶ Suboptimal analgesia for sickle cell pain is common and likely due to a combination of fear of creating opioid dependence as well as negative attitudes by practitioners towards sickle cell patients in the hospital setting.⁵⁴ Morphine, hydromorphone, and fentanyl are all effective. Use of patient-controlled analgesia (PCA) has been shown to be more effective than intermittent injection of opioids for treatment of VOC pain.⁵⁵ For pain relating to VOC, the patient should be treated with a combination of long-acting opioids (continuous intravenous infusion, transdermal patch, or extended-release oral formulation) and a short-acting opioid for breakthrough pain.² Methadone, a unique long-acting opioid with N-methyl-D-aspartate (NMDA) blocking properties, may be useful for perioperative pain in SCD patients with opioid tolerance.⁵⁶

Tramadol interacts with central opioid, catecholamine, and serotonin transmission systems, thereby altering the

perception and response to pain.⁵⁷ Historically, tramadol has been considered advantageous over other traditional narcotics due to less respiratory depression and constipation. Nevertheless, addition of tramadol to a traditional morphine/ketorolac mixture in patients presenting with VOC due to SCD did not lower the amount of daily consumed morphine and did not influence pain scores, duration of PCA use, length of hospital stay, and respiratory rate.⁵⁷

Multimodal analgesia with non-opioid adjuncts can reduce perioperative opioid consumption and may be useful in SCD patients with postoperative or VOC pain. Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are the most commonly used analgesics for mild to moderate pain in sickle cell patients. The effects of acetaminophen are mediated primarily centrally, with minimal peripheral anti-inflammatory action.⁵⁴ Nonsteroidal anti-inflammatory drugs offer significant peripheral anti-inflammatory activity, but they have a ceiling effect.⁵⁴ Moreover, studies examining the efficacy of using NSAIDs specifically for the treatment of VOC pain show conflicting results.^{58,59} Furthermore, it may be prudent to avoid NSAIDs because of the risk of renal injury in patients predisposed to renal dysfunction. Acetaminophen is safe and effective for postoperative pain, though its role in VOC pain is uncertain.

Ketamine is an NMDA antagonist which, in subanesthetic doses, is a safe and effective analgesic that reduces perioperative opioid consumption.⁶⁰ It may also mitigate opioid tolerance and opioid-induced hyperalgesia, which are common in patients with SCD. Emerging studies suggest that low-dose ketamine may be effective for reducing opioid consumption in patients with VOC pain.⁶¹ Dexmedetomidine, anticonvulsants (e.g., gabapentin and pregabalin), and antidepressants (e.g., amitriptyline and duloxetine) are widely used in multimodal analgesia to reduce perioperative opioid consumption, though studies are lacking on use of these drugs specifically in patients with SCD and VOC pain.^{54,62,63} Several retrospective studies and case reports have shown the efficacy of epidural analgesia in treating sickle cell pain in pediatric patients who are resistant to traditional narcotic therapy.^{64,65} Table 4 summarizes a possible strategy and general considerations for effective pain management in sickle cell patients.

Sickle cell disease in pregnancy

Pregnant SCD patients are predisposed to a sickle cell crisis for a number of reasons, including physiologic anemia of pregnancy, increased oxygen consumption, increased stasis in the circulatory system, aortocaval compression, and general inactivity. In addition,

parturients tend to be more hypercoagulable and are more prone to infection due to compromised immune function.⁶⁶ Approximately 55% of sickle cell parturients experience one episode of VOC during pregnancy, while an estimated 43% experience complications, including respiratory infections, kidney failure, septic arthritis, and strokes.^{66,67} Historically, there has been high morbidity and mortality in sickle cell patients who become pregnant. Due to improved understanding of the disease process and treatment options available, the maternal, fetal, and perinatal mortality has declined.⁶⁶ The higher incidence of placenta previa and placenta abruption is a concern, as these complications can lead to fatal hemorrhage.⁶⁸ Patients with sickle cell trait are less affected by pregnancy, as they tend to sickle when the PaO₂ approaches 15–20 mmHg, which is rarely observed.⁶⁶ The advantages of transfusion therapy in parturients have not been settled. Cunningham *et al.* reported a sevenfold reduction in perinatal mortality and decreased maternal morbidity in patients who received prophylactic blood transfusions.^{66,69} Koshy *et al.* reported a decline in sickle cell crisis events but no enhanced benefit to perinatal survival in parturients who received blood transfusions.^{66,70} El Shafei *et al.* showed no difference in maternal and perinatal outcomes when comparing two groups of pregnant sickle cell patients—one group with prophylactic blood transfusions vs the other group without blood transfusions.⁷¹ Anesthetic considerations for a labouring sickle patient should focus on minimizing circumstances that promote sickling events. Several case reports and publications involving children have highlighted the analgesic benefits of neuraxial anesthesia in ameliorating VOC.^{64,65,72} The resulting benefits of the sympathectomy (improved blood flow) must be weighed against the risks of hypotension.^{66,73} Rates of Cesarean delivery are higher in sickle cell patients.⁷⁰ It is critical to maintain appropriate operating room temperatures and to use forced-air warmers and fluid warmers to prevent onset of hypothermia. Due to the added risk of placenta previa, optimal vascular access should be obtained, and rapid infusing devices should be immediately available in the event of massive hemorrhage. Neuraxial anesthesia is acceptable provided practitioners ensure appropriate hydration to prevent hypotension from the ensuing sympathectomy. Care must be taken to avoid higher than necessary spinal levels of anesthesia due to the risk of hypoventilation, respiratory acidosis, and hypoxia, all of which can trigger a sickle crisis.⁶⁶

Summary

Sickle cell disease is relatively common with wide-ranging multi-organ consequences. Patients with sickle cell disease

Table 4 Strategy and considerations for pain management in sickle cell disease**Strategy**

Step 1: Define the nature of the pain

1. Surgical pain: consider regional, neuraxial, or local tissue infiltration techniques
2. VOC pain: oxygen, hydration, keep the patient warm

Step 2: Analgesic options:

- 1st line: Oral opioids, acetaminophen, +/-NSAIDs
- 2nd line: Intravenous opioid PCA, acetaminophen, +/- NSAIDs
- 3rd line: Intravenous opioid PCA, low-dose ketamine infusion and/or gabapentin

Considerations for significantly opioid-tolerant patients with sickle cell disease

- Higher than usual opioid doses will usually be necessary via intravenous PCA
- Calculating baseline opioid requirements in morphine equivalents may be helpful for gauging starting PCA doses (we favour www.glophRPh.com, an online calculator)
- Starting at lower doses and titrating upwards is the safest approach
- Consider using a basal rate on the PCA in addition to the demand dosing
- If possible, simply continue home opioid regimen and add additional opioids as needed
- Consider adjuncts, such as acetaminophen, NSAIDs, ketamine, and gabapentin

NSAIDs = nonsteroidal anti-inflammatory drugs; PCA = patient-controlled analgesia; VOC = vaso-occlusive crisis

are living longer, in part due to hydroxyurea therapy and more aggressive prevention and management of SCD complications. Therefore, SCD patients are encountered with increasing frequency in the perioperative setting. Risk factors unique to SCD surgical patients include the frequency and severity of SCD complications, including infections and recent hospitalizations. Of particular concern are the SCD-related microvascular occlusions and tissue infarctions that lead to organ dysfunction.^{4,16,31,33,39,43,74}

While chronic transfusion of blood may decrease the incidence of stroke, it is less clear whether routine perioperative transfusions confer additional advantage.^{44,45} Ultimately, it is advisable to individualize preoperative transfusion practice by carefully weighing the risks and benefits of transfusion.

When choosing regional vs general anesthesia, it is essential to consider the patient's underlying medical condition, proposed surgery, and potential for postoperative pain—as is the case for all types of surgical patients. There are insufficient data to advocate for one type of anesthetic plan for patients with SCD *per se*, provided that the overall goals of appropriate hydration, blood pressure control, normal acid-base balance, normothermia, analgesia, and anxiolysis are achieved. It is crucial that the anesthesia plan focus on preventing and alleviating vaso-occlusive episodes during the perioperative period.^{25,48}

It is important to distinguish acute postoperative pain from chronic sickle cell pain and pain due to VOC. Treatment of pain includes rest, warmth, analgesia, intravenous fluids, antibiotics, and analgesics.⁴ Opioids

are a mainstay for treatment of pain from VOC and should be used without hesitation in the postoperative period.¹⁶ Multimodal analgesia in the perioperative setting using non-narcotic agents (e.g., NSAIDs, acetaminophen, ketamine, anticonvulsants, and anti-depressants) can be extremely useful, while being careful to identify contraindications due to pre-existing organ dysfunction.^{33,58-61}

Conflicts of interest None declared.

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