

Sickle Cell Disease and Elective Cholecystectomy

PA Leake¹, JP Toppin¹, L King², M Reid³, P Scott⁴, ND Duncan¹, MEC McFarlane¹

ABSTRACT

Patients with sickle cell disease (SCD) are high-risk for perioperative morbidity and mortality. The establishment of guidelines in the management of cholecystectomy, one of the most common surgical procedures in the sickle cell population, will form the basis for streamlining care, nationally. The guidelines were established based on current literature on perioperative care of the sickle cell patient, taking into account local and regional data. The team included general surgeons, anaesthetists, internists specializing in SCD and pulmonologists. Areas of particular focus include patient selection, preoperative transfusion, oxygenation/ventilation, infection control, thromboprophylaxis and postoperative pain control.

Keywords: Cholecystectomy, guidelines, sickle cell, surgery

West Indian Med J 2019; 68 (Suppl. 2): 3

Summary of guidelines

A. Patient selection

1. Cholecystectomy is recommended for patients with sickle cell disease who are symptomatic of gallstones *ie* abdominal pain due to gallstones, choledocholithiasis, prior episode of acute cholecystitis or acute pancreatitis.
2. Patients with sickle cell and physicians should be sensitized to the need for early diagnosis and prompt treatment of symptomatic gallstones.
3. Where possible, hepatobiliary imminodiacetic acid (HIDA) scan during an acute attack of abdominal pain may assist in confirming the diagnosis of symptomatic cholelithiasis.
4. Sickle cell patients should have cholecystectomy performed at a tertiary level institution that possesses an intensive care unit.

B. Preoperative assessment

1. Sickle cell patients who are scheduled for cholecystectomy should be referred to the internal medicine (pulmonology) clinic for preoperative assessment.

2. Internal medicine/pulmonology should be involved in the patient's management on admission to hospital.

C. Hydration

1. Admission solely for hydration is not necessary in sickle cell patients undergoing elective cholecystectomy.
2. Liberal oral fluids should be encouraged, with intravenous fluids only administered overnight.
3. Nil per os (NPO) status can be instituted four hours prior to surgery.
4. All attempts should be made to ensure that sickle cell patients are the first on the operating list.

D. Blood transfusion

1. Simple whole blood transfusion to 10 g/dL is recommended for sickle cell patients undergoing elective cholecystectomy, if presenting haemoglobin is 8 g/dL or less.
2. No blood transfusion should be given if haemoglobin is above 8 g/dL and represents the patient's steady state.

From: ¹Department of Surgery, Radiology, Anaesthesia and Intensive Care, Faculty of Medical Sciences, ²Sickle Cell Unit, Caribbean Institute for Health Research, ³Caribbean Institute for Health Research and ⁴Department of Medicine, Faculty of Medical Sciences, The University of the West Indies, Mona, Kingston 7, Jamaica, West Indies.

Correspondence: Dr PA Leake, Department of Surgery, Radiology, Anaesthesia and Intensive Care, Faculty of Medical Sciences, The University of the West Indies, Kingston 7, Jamaica, West Indies. Email: paeleake@yahoo.com Caribbean Institute for Health Research

3. If transfusion is indicated and not administered, such action needs to be justified by the managing physician.
- E. Oxygenation/ventilation
1. All patients with sickle cell disease scheduled to undergo cholecystectomy should undergo preoperative pulmonary function tests.
 2. Chest physiotherapy should be commenced in the preoperative period.
 3. Pulse oximetry must be a part of vital sign monitoring of sickle cell disease patients.
 4. Timing of discharge should be coordinated between medical and surgical teams.
 5. Patients should be discharged with some form of incentive spirometry device.
- F. Temperature regulation
1. Methods to maintain normothermia should be used intra- and postoperatively, including forced air warmers and warmed intravenous fluid.
- G. Infection control
1. All patients with sickle cell undergoing cholecystectomy should be given antibiotic prophylaxis.
- H. Pain control
1. A plan for postoperative pain management should be determined by the anaesthetic team during their preoperative assessment.
 2. Postoperative pain should be controlled with regular opioid analgesia.
 3. Parenteral or oral morphine (as patient condition allows) is the drug of choice.
 4. Additional analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen should be administered regularly.
 5. Dosing of analgesia should be appropriate to the patient's level of pain.
 6. As necessary (prn) dosing should also be included in the patient's analgesia regime.
 7. Adjunctive measures for opioid sparing, such as transversus abdominis plane block, are recommended.
 8. The use of a pain scale to assess pain level should be incorporated as part of the patient's vital sign monitoring.
- I. Deep vein thrombosis (DVT) prophylaxis
1. All sickle cell patients undergoing cholecystectomy should be given pharmacologic DVT prophylaxis.

INTRODUCTION

Sickle cell disease (SCD) is an inherited haemolytic disorder that affects 1 in 150 newborns in Jamaica (1). Owing to red blood cell haemolysis, these patients are predisposed to the development of gallstones, with rates of up to 83% in the adult population (2). The current standard of care for the treatment of symptomatic gallstones is laparoscopic cholecystectomy (3), with some reports suggesting that asymptomatic gallstones should be managed similarly in the sickle cell population (4).

Patients with sickle cell are prone to significant morbidity and mortality related to surgery and anaesthesia. Changes in temperature, oxygen tension and fluid volume related to the surgical process predispose patients with SCD red cell sickling intra- and postoperatively with consequent vaso-occlusive crises (5). The most notable SCD-related postoperative complications include acute chest syndrome, painful crises, stroke and priapism.

Perioperative morbidity rates of 7% to 14% have been reported internationally, most of which are SCD-specific (6–8). Rates of acute chest syndrome have been quoted as 0.4% to 10% (9). Mortality rates of less than 1% have been reported from high-volume centres (10, 11). Significantly higher morbidity rates have been quoted in the Caribbean – 44.4% by Leake *et al* (12), 37.5% by Plummer *et al* (13) and 21% by Dan *et al* (14).

Multiple factors that contribute to red cell sickling have been established. The UWI/UHWI guidelines for SCD and cholecystectomy have been developed based on detailed examination of the literature and international guidelines, taking into account national factors. The guidelines focus on strategies to prevent red cell sickling and the morbidity and mortality associated with vaso-occlusive crises.

Patient selection

Patient selection for cholecystectomy is an important decision. Recent papers have justified prophylactic cholecystectomy in both the paediatric and adult SCD populations based on reduced morbidity rates for elective surgery in the prophylactic patient group as compared to the symptomatic group (4, 15). In the Sickle Cell Jamaican cohort study, the natural history of gallstones shows low conversion to symptomatic cholelithiasis (16). In addition, the present morbidity rate is extraordinarily high (12, 13). Such a disparity between risk and benefit does not justify prophylactic cholecystectomy at present. Elective cholecystectomy should therefore, be

reserved for symptomatic gallstones and should include the following patients:

- a) Patients with right upper quadrant signs and symptoms attributed to gallstones
- b) Patients with findings consistent with choledocholithiasis
- c) Patients with a prior episode of acute cholecystitis or acute pancreatitis
- d) Symptomatic patients with an abnormal hepatobiliary immino-diacetic acid (HIDA) scan
- e) Patients with ultrasound findings consistent with cholecystitis

The key to effective surgical management of sickle cell patients with biliary pathology must be timely surgical referral. Physicians managing sickle cell patients must be sensitized to the need for early diagnosis and treatment and the methods available to distinguish gallstone-related symptoms from other SCD-related complications. In so doing, patients can be managed prior to the development of possible life-threatening biliary complications.

With a number of sickle cell disease-related abdominal complaints that mimic symptomatic cholelithiasis, it can be difficult to make the diagnosis. This challenge often leads to delays in surgical referral. The use of the HIDA scan, which confirms cystic duct obstruction during an acute episode of abdominal pain, can assist in confirming biliary colic. It has the advantage over abdominal ultrasound in being a functional investigation that evaluates filling of the gall bladder as opposed to structural abnormalities that may not be present even in symptomatic patients.

Owing to the high-risk nature of surgery in the SCD population, we recommend that all surgical follow-up of SCD patients with gallstones and surgical procedures or endoscopic interventions be undertaken at a multidisciplinary tertiary-level hospital with an intensive care unit.

Preoperative assessment, oxygenation and ventilation

Patients with SCD undergoing surgery should be considered high-risk. A significant proportion of these patients have underlying pulmonary pathology that contributes to their high postoperative risk. Fonseca *et al* (17) demonstrated that 78% of their cohort had abnormal pulmonary function. Preoperative measures to optimize pulmonary function and improve outcomes must be employed. This involves a coordinated, multidisciplinary assessment. Prior to surgery, patients with sickle cell should be referred to the pulmonology/internal medicine clinic for a complete pulmonary assessment.

Pulmonary complications are responsible for major postoperative morbidity and mortality in SCD patients (12). Acute chest syndrome occurs in up to 10% of postoperative patients. Although it is not possible to predict which patients will develop postoperative sickle cell-related complications, preoperative optimization of pulmonary function is likely to improve postoperative outcomes.

Preoperative pulmonary evaluation should include the assessment of functional residual capacity, a measure of the ability to increase and maintain tissue oxygen delivery (18), spirometry and baseline pulse oximetry. Pulse oximetry is a useful measure in assessing readiness for discharge and should therefore, be a part of the normal vital signs charting in a patient with sickle cell. Patients with saturations below that of baseline would need further monitoring, evaluation and optimization prior to discharge.

International guidelines stress the importance of perioperative chest physiotherapy, along with incentive spirometry, in the management of the sickle cell patient. Incentive spirometry has been shown to reduce atelectasis and acute chest syndrome in patients with sickle cell disease (19, 20). This therapy should be extended post-discharge with incentive spirometry continuing at home.

Hydration

Dehydration contributes to red cell sickling and potentiates perioperative complications in patients with sickle cell disease. Ensuring adequate hydration in the perioperative period is essential. Admitting patients for the sole purpose of intravenous fluid administration is not necessary, although most patients would require preoperative admission for blood transfusion and preoperative physiotherapy.

Judicious fluid management is required in SCD patients to both prevent dehydration and fluid overload. In order to ensure fluid homeostasis, liberal oral fluids are encouraged. The administration of intravenous fluids becomes necessary once the patient is no longer allowed to drink. Over time, the fasting period prior to anaesthesia has changed, with most guidelines now suggesting a fasting period of two to four hours (21).

If possible, patients with sickle cell disease should be first on the operating list. This ensures that long periods of preoperative fasting are not required and that all support staff, including those required for postoperative care (*eg* physiotherapy) are available.

Transfusion

Preoperative blood transfusion, in an effort to improve oxygen delivery and reduce red cell sickling, has been explored as a measure to improve patient surgical outcomes. In addition, the type of transfusion – conservative or aggressive (exchange transfusion) has been evaluated.

Current national and regional policies do not support preoperative transfusion in patients with sickle cell, as demonstrated by the 3.7% transfusion rate in a recent local study and 0% transfusion in previous regional reports (12, 14) of patients with sickle cell undergoing cholecystectomy. Of note, most international reports evaluating outcomes of patients with sickle cell undergoing cholecystectomy include preoperative transfusion with rates of 57.4–92% (6–8, 22).

Transfusion or no transfusion

Most studies support some form of preoperative transfusion. Haberkern *et al* (23) reported on 364 patients undergoing cholecystectomy. The highest rate of postoperative sickle cell events was noted in the non-transfusion group (32%). More recently, Howard *et al* (24) conducted a randomized trial of 67 patients. They found significantly higher complication rates in the no-transfusion group (39%) compared to the preoperative transfusion group (15%).

Systematic reviews and meta-analyses of randomized trials have failed to show an advantage of preoperative transfusion. The studies, however, were underpowered to detect a treatment effect (25, 26). Further studies are ongoing.

Simple transfusion or exchange transfusion

Studies evaluating the value of exchange transfusion (decreasing haemoglobin S levels) have demonstrated that a conservative approach (increasing haemoglobin levels) is sufficient in improving patient outcomes. Vichinsky *et al* (9) found a higher rate of transfusion-related complications in the aggressive transfusion group (14% *versus* 7%) in a randomized trial and concluded that a conservative transfusion regime was preferable. A recent meta-analysis of randomized trials has failed to demonstrate superiority or inferiority of exchange transfusion over simple transfusion (26). In addition, exchange transfusions, particularly for adults, require a large amount of blood – a resource that is often scarce in our environment.

Based on this evidence, the preoperative strategy of simple transfusion has been included in the current guidelines. We have limited transfusion to patients with

severe anaemia as evidence suggests that patients without severe anaemia, can develop hyperviscosity, with ensuing vaso-occlusion, if given a “top-up” transfusion (26).

Temperature regulation

The effect of hypothermia on red cell sickling and vaso-occlusive crises is well established (27). The surgical environment, however, is not conducive to maintaining normothermia. Operating theatre temperatures are expected to be 21 °C to 24 °C in order to reduce infectious complications (28). In addition, patients are fully exposed on a cold operating table leading to significant evaporative and conductive heat losses.

Ensuring measures are instituted intra- and postoperatively to maintain normothermia is an essential part of perioperative management. The use of warmed intravenous fluids and forced air warmers are recommended in the operating room and recovery room (29). Where possible, the temperature of the operating theatre should be kept close to 24 °C prior to induction, preparation and application of warmers (30). On the ward, patients should be kept warm with blankets and warm clothing, if necessary.

Infection control

The current guideline for the use of prophylactic antibiotics for elective open cholecystectomy is the administration of a single dose of first-generation cephalosporin within one hour prior to the skin incision (31). Routine continued administration of antibiotic in the postoperative period has been abandoned, as it is associated with adverse reactions, the emergence of drug-resistant strains and unnecessary financial costs (32). Elective laparoscopic cholecystectomy carries a significantly lower-risk of wound infection hence the use of prophylactic antibiotics is not justified in patients undergoing elective, uncomplicated laparoscopic cholecystectomy (31).

Patients with sickle cell disease are considered to be immunocompromised from an early age because of autosplenectomy from multiple splenic infarctions. Because infections are often a precursor for complications in patients with SCD, prophylactic antibiotics are recommended in routine cholecystectomy (23, 33, 34).

The Tokyo Guidelines 2018 (TG18) outlines recommendations for the appropriate use of antimicrobials for patients undergoing treatment for acute cholecystitis. The recommended antimicrobial agents are empirical agents used before organisms are identified. Antimicrobial

agents are chosen based on the local profile of antibiotic susceptibility and resistance in each hospital (35). Patients with SCD are considered to be high-risk and would also receive prophylactic antibiotics prior to cholecystectomy for acute cholecystitis and for all attacks of acute cholecystitis treated non-operatively.

Pain control

The management of acute postoperative pain presents a challenge to all healthcare professionals involved in the management of these patients. Most surgical patients will experience suboptimal management of post procedural pain. In addition to the associated patient suffering and decreased patient satisfaction, postoperative pain can result in delayed patient mobilization, atelectasis, respiratory dysfunction and prolongation of hospitalization. Patients with SCD undergoing even relatively minor surgery may be at increased risk of suboptimal pain control and be at increased risk of life-threatening respiratory complications such as acute chest syndrome, potentiated by poor pain control.

Preoperative assessment

A plan for the pain management of these patients should be included in the preoperative assessment by the anaesthesia service. This should include a review of the patient's pain history, addressing the nature of previous vaso-occlusive crises, chronic pain syndromes and ongoing needs for analgesia.

Intra-operative management

Specific details about the intra-operative pain management will be left to the discretion of the responsible anaesthetic team and consultant anaesthetist. Opioid-sparing techniques are encouraged and when applicable may include the use of non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, regional blocks such as transversus abdominis plane block and local anaesthesia infiltration at the port sites (36, 37).

Postoperative pain management

Assessment of pain control/Use of pain scores

For the first 48 hours, pain control should be evaluated using the numerical rating scale (NRS) and this value recorded as part of the patient's vital signs (36).

Recovery room

The NRS should be evaluated and documented in the recovery room as soon as the patient is awake and

coherent enough to do this. The score should also be documented at the time of discharge from the recovery room. Patients should require NRS scores of < 3 to be discharged to the ward. Again, details of the specific analgesics used in the recovery room will be determined by the responsible anaesthesia team.

Analgesic plan for use on the ward

This plan should be developed by both the surgical and anaesthesia teams involved in the care of the patient. Patients with higher requirements for analgesia and/or those with more complicated pain histories (*ie* history of chronic pain) should be identified and these patients receive ongoing evaluation of their pain control by the anaesthesia service on the ward. The NRS should be evaluated and documented every six hours for the first 24 hours and every eight hours for at least the subsequent 48 hours.

Specific recommendations:

- 1) Morphine
 - a. Use of morphine as the first line opioid for the immediate postoperative period.
 - b. We recommend the use of the subcutaneous route during the initial postoperative period.
 - c. When oral intake has been restarted, oral morphine can be used.
 - d. During this initial period, morphine should be given regularly every four hours (unless there is impaired clearance of the drug *eg* renal dysfunction), and there should be the option to give additional medication for break-through-pain.
 - e. Pethidine can be substituted at equivalent doses.
- 2) Adjuncts
 - a. Adjuncts used intra-operatively should be continued in the postoperative period.
 - b. Where feasible, they can be given parenterally and switched to oral administration when appropriate.
 - c. Rectal medications can be utilized (paracetamol or NSAIDs).

Deep vein thrombosis prophylaxis

Sickle cell disease is associated with an underlying hypercoagulable state, which contributes to its disease pathology and an increased risk for venous thromboembolism [VTE] (38). Studies have shown VTE prevalence

rates up to 25% in SCD patients (39). Additionally, cumulative incidence of VTE to age 40 years of 11.3–12.5% has been noted (40, 41). Studies have been fairly consistent in demonstrating a two to three-fold increased mortality risk in persons with VTE compared to those without (39–41).

A number of risk factors have been identified for VTE in SCD. These include age, gender, pregnancy / postpartum period, hospitalizations, genotype and severe SCD [≥ 3 admissions per year] (39–43). The median age for first VTE (27.8 to 31 years) in SCD has been shown to be younger than that of the general population in persons with severe genotypes, Hb SS or SB0 thalassemia (39–41). Females with SCD have been shown to have a 22% higher-risk for VTE; this risk remains higher independent of pregnancy status (40). Bruson *et al* (40) also showed a higher incident rate (14.0 per 1000 patient-years) of VTE with severe SCD (defined as ≥ 3 admissions per year) compared to less severe disease (4.6 per 1000 patient-years).

For surgical procedures that carry a high-risk for VTE, such as major orthopaedic surgery, pharmacologic thromboprophylaxis (PTP) is generally recommended. In lower-risk surgeries such as laparoscopic cholecystectomy where incidence of VTE is lower (44), the clinical benefit of PTP remains unclear and may increase risk for postoperative bleeding (45). At present, there are no guidelines for VTE prophylaxis in SCD currently or studies to inform anticoagulant practices. Thus, decisions on prophylaxis must be based on extrapolation from the general population.

Generally, PTP recommendations for surgery often rely on individual assessment of risk. With awareness of the risk factors associated with SCD, it seems prudent that SCD undergoing cholecystectomy should be given PTP.

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