Anaesthesia for patients with sickle cell and other haemoglobinopathies

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Learning objectives

After reading this article, you should be able to:

- understand the pathophysiology of sickle cell disease
- identify the systemic manifestations and treatment options of sickle cell disease
- recognize the need for a multidisciplinary approach during the perioperative period in patients with haemoglobinopathies

Abstract

Sickle cell disease is an autosomal recessive multi-systemic condition, caused as a result of a mutation in chromosome 11 resulting in production of abnormal beta globin of haemoglobin or HbS. The abnormality under specific conditions results in polymerization of the globin chain resulting in deformed sickle-shaped red cells. These haemolyse under adverse conditions resulting in occlusion within the circulatory system resulting in cardiorespiratory, neurological, renal, musculoskeletal and bone marrow dysfunction, along with increased susceptibility to infections leading to significant morbidity and mortality. The perioperative period provides the perfect milieu for exacerbations and careful attention to the fundamentals of oxygenation, analgesia, hydration, antibiotic prophylaxis and temperature control are the key preventative strategies utilized in this setting. Hydroxyurea, blood transfusion and haematopoietic bone marrow transplant are the available options for treatment.

Keywords Anaemia; anaesthesia; haemoglobinopathy; hydroxyurea; sickle cell

Royal College of Anaesthetists CPD Matrix: 1A01, 1A02, 2A03, 2A05

Sickle cell disease

Introduction

Adult haemoglobin comprises of four globin chains. The majority of haemoglobin is in the form of haemoglobin A (HbA >90%) with two α and two β globin chains, haemoglobin A2 (HbA2 < 5%) with two α and two δ chains and fetal haemoglobin (HbF < 2–3%) with two α and two γ chains.

Sickle cell disease (SCD) refers to a group of congenital disorders that lead to the formation of structurally abnormal haemoglobin molecules. SCD results from a mutation on chromosome 11, which causes an amino acid substitution, valine for glutamic acid, on the β globin subunit of HbA leading to the production of haemoglobin S (HbS).

SCD is an inherited autosomal recessive condition. Individuals who inherit this abnormal gene from both parents (homozygous HbSS) have a severe form of SCD, often referred to as sickle cell anaemia in which the majority of haemoglobin is HbS. The heterozygous state is known as sickle cell trait or a carrier state (HbAS). Of note, it is also possible that together with HbS from one parent, another haemoglobin variant (HbC, thalassaemia) may be inherited from the other parent leading to a number of other sickling disorders (HbSC or HBS-thalassaemia, etc.).

Although there is a lack of reliable international data regarding estimates of incidence and prevalence of SCD, it is widely acknowledged to be an increasing global health problem with an estimated 300,000 infants being born with the homozygous state each year.[1] The vast majority of newborn babies with SCD are born in Africa, the Mediterranean, Middle East and parts of India; however, the number of patients with SCD is thought to be increasing in all countries. In the UK, it accounts for almost 250 births annually.[2] Life expectancy and causes of mortality vary significantly between high-income and low-income countries with access, cost and availability the main barriers to gaining effective treatment.

Pathophysiology

HbS is biochemically unstable and relatively insoluble. When deoxygenated, HbS polymerizes, damaging the erythrocyte and causing it to lose cations and water. The resulting polymers align into bundles, causing distortion of the RBC into a crescent or sickle shape, decreasing their half - life, and reducing flexibility and deformability, which impairs passage of the cells through narrow blood vessels. This results in vascular occlusion and haemolytic anaemia, two characteristic features of SCD. Homozygous cells begin to sickle at much higher oxygen saturation, typically 85% (PaO_2 5.2–6.5kPa) than heterozygous cells at 40% (PaO_2 3.2–4.0 kPa).[3] Sickling with sickle cell trait is therefore rarely a problem without concomitant stasis and patients with sickle cell trait are invariably healthy.

Traditionally, it was thought that a trigger, such as hypoxia, led to sickling, precipitating further flow impairment, stasis and acidosis leading to a 'vicious cycle' of further sickling ending in ischaemia, infarction and end organ damage.[4] Stress, hypothermia, alcohol abuse and dehydration are some other states, which favour stasis and promote sickling. However, it has now been shown that a number of other pathological and interrelated processes simultaneously occur. These include vascular-endothelial dysfunction, functional nitric oxide deficiency, inflammation, oxidative stress and reperfusion injury, hypercoagulability, increased neutrophil adhesiveness and platelet activation. Any one of a variety of possible factors may cause endothelial activation leading to vascular occlusion, thus

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sickling may occur as a secondary event rather than the initial trigger.

Bacterial infection remains a significant cause of morbidity and mortality due to splenic dysfunction, an ischaemic environment, impaired phagocytic function of macrophages and cytokine release.[5]

There is a high degree of clinical heterogeneity amongst patients with similar haemoglobin genotypes. The precipitants of SCD do not have uniform effects, episodes of vascular occlusive are unpredictable, the rate of haemolysis is variable and the frequency of chronic complications is not always easily explained.

Diagnosis

The diagnosis of sickle cell disorders can take place in multiple settings including prenatally, newborn screening, testing of symptomatic individuals and incidental findings. Prenatally, diagnosis can be made from DNA obtained via chorionic villus sampling or amniocentesis. Heel prick testing of newborns is routinely carried out in the UK as part of the NHS newborn blood spot-screening programme. Of note, testing may be unreliable in extreme prematurity or following blood transfusion. The sickledex test may be used as a rapid screening tool to identify the presence of HbS, however it is unable to distinguish between sickle cell trait and SCD. Haemoglobin analysis, by electrophoresis, remains necessary and is the gold standard to confirm the diagnosis.[6]

Clinical features

The clinical features of SCD and the relevant investigations are highlighted in Table 1.

A significant number of these features are seen with the severe or homozygous form of the disease.

Management

A haematologist at a specialist centre should follow up all patients with SCD. General advice is to educate patients, together with parents where necessary, regarding avoidance of activities that may lead to dehydration, stress, exposure to extreme temperatures, exhaustion as well as the harmful effects of smoking and alcohol. Additionally, palpation for splenic size to encourage early presentation of splenic sequestration crisis has been suggested to be of benefit.

Routine blood tests are important to establish baseline values, which may be abnormal. Folate and vitamin D levels should be checked as supplementation may be required. Infection prevention is of vital importance. Oral penicillin prophylaxis is started at the time of diagnosis. Routine childhood vaccinations including protection against *Haemophilus influenza* type B, *Streptococcus pneumoniae*, *Neisseria meningitides*, hepatitis B and seasonal influenza are offered. From the age of 2 unconjugated pneumococcal vaccination is needed and malaria prophylaxis must also be considered when appropriate. There is an increased susceptibility to infections by encapsulated bacteria and as such, fever in a patient with SCD should be urgently assessed by a medical professional, cultures taken and appropriate antibiotics started.

Hydroxycarbamide (hydroxyurea — HU) is currently the only approved pharmacological treatment for SCD. Despite its longstanding use, the understanding of its mechanisms of action remains incomplete. It inhibits ribonucleotide reductase, which leads to inhibition of DNA synthesis and cellular cytotoxicity. It causes increased fetal haemoglobin (HbF) production and decreased production of HbA, thus the overall effect is to decrease the concentration of HbS. It is given as a once daily dose (15—35 mg/kg/day) and evidence supports its use to reduce the risk of acute pain and the acute chest syndrome as well as being effective in primary stroke prevention. The major side effect is myelosuppression, which must be monitored. Other side effects include weight gain, hyperpigmentation and azoospermia. Erythropoietin (EPO) has also been used alongside HU for management of anaemia.

Primary stroke prevention is addressed by annual transcranial Doppler ultrasonography between 2 and 16 years of age. Abnormal findings are frequently treated with red blood cell transfusion (simple top up or an exchange transfusion where blood from the affected individual is taken and replaced by blood from a healthy donor). The aim of blood transfusion is to decrease the concentration of HbS to <30%. Blood transfusion can be used for both therapy and prophylaxis. Prophylactically, it is given to children at risk of first stroke in twin pregnancy or pregnancy with past history of medical obstetric and fetal complications, and before high risk cardio thoracic, neurological or abdominal surgery. Transfusion is readily used during sequestration crises, in multi-organ failure and in severe sepsis. During acute painful crisis, anaemia should not be routinely treated with blood transfusion unless there is an Hb drop greater than 2 g/dl or deteriorating organ function. For emergency surgery, the Hb level, urgency and complexity of procedure needs to be taken into account before transfusion. As a simple rule, transfusion can be given if Hb is <9 g/dl. If simple transfusion (top up) is needed, patients must be given ABO-compatible, extended Rh— and Kelly matched units. In all cases, the risks and benefits of blood transfusion must be carefully considered. Antibodies as a result of multiple transfusions in these patients can pose problems and limit the availability of appropriately cross matched blood.

Haematopoietic cell transplantation (HCT) is potentially curative treatment for SCD. HCT is curative in almost all children who have a human leukocyte antigen-matched sibling donor. Its use is currently restricted by difficulty establishing criteria for patient selection and transplant, together with toxicity and limited availability of suitable donors. SCD continues to have a highly variable clinical course that cannot be easily predicted and furthermore, those with advanced SCD are likely to have pulmonary and neurological disease meaning their transplant-related morbidity and mortality would be increased. Gene therapy using strands of DNA from stem cells to compensate for the affected individuals malfunctioning genes could provide hope for this cohort of patients in the future.

Anaesthetic considerations

Preoperative preparation

A multidisciplinary approach involving the anaesthetist, haematologist and surgeon is essential during the perioperative period. Patients with SCD should have a detailed preoperative assessment with focus on history and examination to assess disease severity. A variety of investigations are likely to be

Clinical manifestations and relevant investigations for SCD

System	Clinical manifestations	Relevant investigations
Neurological	TIA	CT scan, MRI scan
	Stroke	Trans-cranial Doppler
	Posterior reversible encephalopathy	Fundoscopy
	Meningitis	Lumbar puncture
	Retinopathy	EEG
	Blindness	
Cardiac	Hypertension, myocardial Infarction,	ECG, Trop T, NT pro BNP,
	cardiac failure, cardiomyopathy	Echocardiogram, MRI heart
	Arrhythmias	Doppler lower limb
	Recurrent venous thromboembolism	
	Death	
Pulmonary	Chest infections	Sputum culture, PFTs, X-ray chest
	Pulmonary embolism, ARDS	CT thorax, ventilation—perfusion scans
	Pulmonary hypertension, Asthma	CTPA, blood gases
	Acute chest syndrome	
Haematological	Anaemia, aplastic crisis,	FBC, MCV, folic acid, zinc, B12, ferritin, vitamin D
	repeated transfusions, iron overload	Peripheral smear, group and screen,
	Poor vascular access	cross match, bone marrow biopsy
Renal and Genitourinary	Repeated UTI, renal failure,	urine culture, urea and electrolytes
	Papillary necrosis, priapism	Ultrasound kidneys, CT abdomen
Gastro-intestinal	Splenic sequestration crisis,	LFTs,
	Auto-splenectomy, gall stones,	ultrasound abdomen
	Hepatic dysfunction, hepatic sequestration	CT abdomen
Musculoskeletal	Acute and chronic pain, dactylitis	Calcium and phosphate levels
	Vaso-occlusive crisis	Bone scans
	Osteomyelitis	X-Ray
	Avascular necrosis	CT, MRI scan
	Leg ulcers	
Infections	*Streptococcus pneumonia*, *Haemophilus*,	Appropriate cultures, pro-calcitonin
	Neisseria, *Salmonella*,	
	parvovirus, hepatitis B, C, HIV,	
	mycoplasma, chlamydophilia,	
	malaria, *Edwardsiella tarda*	
Pregnancy	Pre-eclampsia, preterm labour, painful crisis, critical care	Ferritin, urinary PCR, ultrasound,
	admission, haemorrhage, transfusion, maternal mortality,	growth scans, fetal fibrinonectin
	increased LSCS rates, still birth, small for gestational age,	
	low birth weight, prematurity	
Others	Delayed puberty, growth restriction anxiety, depression	Thyroid hormone, growth Hormone,
		estradiol, testosterone levels

TIA, transient ischaemic attack; CT, computerized tomography; MRI, magnetic resonance imaging; ECG, electrocardiogram; Trop T, troponin T, NT Pro-BNP, N terminal pro brain natriuretic peptide; ARDS, acute respiratory distress syndrome; CTPA, computerized tomography with pulmonary angiography; PFT, pulmonary function tests; MCV, mean corpuscular volume; UTI, urinary tract infection; LFT, liver function test; HIV, human immunodeficiency virus; LSCS, lower segment caesarean section; PCR, protein creatinine ratio.

Table 1

indicated depending on the type of surgery and end organ damage. A group and screen for antibody and a cross −match is essential for all patients. The need for preoperative transfusion should be discussed with an experienced haematologist. Pain management plans should be discussed with the patient and pain team preoperatively, with a multimodal approach likely to be most appropriate and effective. Starvation time must be minimized and preoperative hydration encouraged with oral and/or intravenous fluids as necessary.

Intraoperative care

Meticulous attention must be paid to the avoidance of triggers that may lead to crisis with emphasis on maintaining good hydration, avoiding hypoxia, replacing blood loss, temperature monitoring with use of active warming and preventing acidosis. Careful patient positioning intraoperatively should be maintained to reduce venous stasis and although arterial tourniquets are not absolutely contraindicated their use should be minimized whenever possible. Antibiotics should be used for surgical

prophylaxis and aseptic techniques during invasive procedures to minimize the risk of infection are mandatory. Anaesthetic agents, sedatives, analgesics and neuromuscular blockade should be titrated depending on the renal function of the individual. Cell salvage is a relative contraindication in SCD but has been used in sickle cell trait.[7]

Postoperative care

There should be a low threshold for patient admission to a critical care unit if necessary. Maintaining oxygen saturation greater than 95% (administering oxygen if necessary), good pain relief, early mobilization, hydration and thromboprophylaxis are essential strategies in the postoperative period. Incentive spirometry and physiotherapy should be utilized if necessary for optimizing pulmonary outcomes. Close communication between all clinical teams is essential throughout the perioperative period.

Prognosis

The prognosis of those with SCD varies greatly. In general terms, however, prognosis has been steadily improving as a result of increased access to comprehensive care. In developed countries, the median age of survival is greater than 60 and death is more frequently caused by end organ damage as opposed to bacterial infection. Despite advances in management strategies, survival of those with SCD lags behind those unaffected and furthermore the quality of life is often poor due to chronic disease processes.

Special circumstances

Pain

Many episodes of acute pain in SCD are managed in the community. Acute pain is caused by vascular occlusion with resulting tissue ischaemia and inflammation. Detailed assessment is important to distinguish this from other sources of somatic and visceral pain. Use of appropriate terminology is necessary as patients and their relatives are likely to have significant experience in recognizing and managing their pain. Each step of the analgesic ladder should be followed, but it is important to bear in mind that those patients who present to hospital are likely to require intravenous opioids. IV morphine (or fentanyl for those with renal impairment) is an appropriate choice, but if repeated doses are required, patient controlled analgesia (PCA) will be needed together with early referral to acute pain services. Attention should be paid to breakthrough pain, hydration status and potential side effects of opioids.

Acute chest syndrome

The acute chest syndrome (ACS) remains a leading cause of morbidity and mortality. It is defined as 'an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest X-ray'. Severe hypoxia is a useful predictor of severity and outcome.[8] The clinical features may be hard to distinguish and in many cases patients present with a painful vascular occlusive crisis and the acute chest syndrome develops within 24–72 hours. Equally, it can occur in the postoperative period. Early involvement of the critical care team to assess the need for respiratory support is vital. Appropriate pain relief, ventilator support to improve oxygenation, exchange transfusion, treatment of infection and thromboprophylaxis forms the mainstay of treatment.

Pregnancy

Risks to both mother and fetus are significantly increased in SCD, and as such preconception assessment and counselling should be performed whenever possible.[9] The patient's partner should be offered screening tests for haemoglobinopathy to determine the risk to future offspring and subsequent genetic counselling. Hydroxycarbamide should be stopped as soon as pregnancy is confirmed. It is also wise to ensure that the patient's immunizations are up to date.

Pregnant women with SCD should be managed in a specialist centre by a joint obstetric and haematology team. As soon as possible, or at the initial booking visit, folic acid, vitamin D and aspirin should be prescribed together with thromboprophylaxis which is likely to be indicated. Any prophylactic antibiotics prescribed prenatally should be continued during pregnancy. If not done prenatally, evidence for end organ damage should be sought through blood tests (FBC, UE, LFT, ferritin, folate), urinary protein to creatinine ratio, echocardiography and retinal screening. In women with high ferritin levels, cardiac MRI should be considered to assess iron loading. Patient education is vitally important, as severe anaemia, urinary tract infections, vascular occlusive crises and transfusion risks are more common in pregnancy.[10] Hyperemesis during the first trimester can trigger dehydration and crises and needs to be dealt with aggressively. More regular antenatal appointments will be necessary including regular screening for asymptomatic urinary tract infection. Finally, it is vital that blood samples are taken to ensure compatible blood is available in the necessary laboratory.

Other haemoglobinopathies

The term 'haemoglobinopathy' encompasses genetic disorders, which are divided into three main groups:[11]

- The thalassaemia syndrome – the main issue here is synthetic disturbance in production of globin chains. Haemoglobin structure is normal.
- Structural haemoglobin disorders – the issue here is altered structure of the globin chain, e.g. HbS, HbSC, HbCC, and HbAC.
- Mixed form – here both the structure and synthesis of the globin chain is altered HbS-thalassaemia, HbE-thalassaemia.

The thalassaemias are a group of conditions inherited in an autosomal recessive pattern. They are characterized by reduced or absent production of one of the two polypeptide chains (α or β) that form the normal adult human haemoglobin molecule, HbA. This abnormal alpha to beta chain ratio causes the unpaired chains to precipitate and causes ineffective erythropoiesis and haemolysis. β-Globin gene defects may give rise to beta thalassaemia, while mutations of the α-globin gene may cause alpha thalassaemia. There are many forms and its clinical severity varies enormously.

Thalassaemia is often classified according to clinical phenotype and β thalassaemia is therefore major, intermedia or minor which corresponds to severity of disease being greater as the amount of functional globin chains is reduced. Beta thalassaemia major (also known as Cooley's anaemia) is caused by homozygosity and affected individuals have profound and lifelong transfusion dependent anaemia. Symptoms typically begin in late infancy as fetal haemoglobin is replaced. Children present with:

- failure to thrive
- anaemia
- jaundice
- hepato-splenomegaly
- bone expansion secondary to extra medullary erythropoiesis - potentially leading to a difficult airway
- iron overload
- cardiac arrhythmias.

Mortality is high without treatment, but in a similar fashion to SCD, prognosis is improving in areas in which early diagnosis and aggressive treatment are available and accessible.

Beta thalassaemia intermedia encompass a wide range of presentations but generally affected individuals are anaemic but not transfusion dependent during childhood. The anaemia will be hypochromic and microcytic with a high RBC count and can be distinguished from iron deficiency anaemia by normal iron levels. Beta thalassaemia minor is often an asymptomatic carrier state.

There are four genes encoding for alpha chain production and therefore many possible combinations of alpha thalassaemia genotypes. The absence of four alpha chains leads to severe anaemia during fetal development with fetal hydrops and is incompatible with live birth. This is known as haemoglobin Bart's. When three genes are inactive the condition is called as HbH. Beta chains precipitate leading to formation of Heinz bodies. Anaemia, gallstones, hepatosplenomegaly, leg ulcers and folic acid deficiency are hallmarks.

Viral infections and certain oxidant drugs can precipitate crises. Minor alpha thalassaemia results when two genes are inactive and a silent form with barely noticeable anaemia occurs when one gene is inactive. Treatment options of the major forms include bone marrow transplant, blood transfusions, iron chelating agents and splenectomy.

The minor thalassaemia, in general, should not cause significant problems during anaesthesia in either elective or emergency surgery. Patients with β thalassaemia major do warrant special attention. A similar approach to that of a patient with SCD is recommended, with a careful history, examination and systems based consideration of potential organ damage often caused by iron overload. Additionally, those with thalassaemia major may be more likely to have a difficult airway due to bone marrow hyperplasia. ◆

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