

# ANAESTHETIC MANAGEMENT OF SICKLE CELL DISEASE IN CHILDREN

## ANAESTHESIA TUTORIAL OF THE WEEK 153

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### SELF-ASSESSMENT QUESTIONS

Before continuing, try to answer the following questions. Choose the *single* best answer. The answers can be found at the end of the article.

1. Normal adult red blood cells contain:
  - a. HbA, HbAS, HbF, HbS
  - b. HbA, HbA2, HbF
  - c. HbA, HbF, HbS
  - d. HbA1, HbA2, HbF
  - e. HbA, HbAS, HbFS, HbF
2. Sickle cell disease is most commonly found in which populations:
  - a. Southern Africa
  - b. India and Asia
  - c. Caribbean and West Africa
  - d. North America
  - e. Southern Europe
3. What is the most common site for a painful crisis in a patient with sickle cell disease?
  - a. Head and neck
  - b. Abdomen
  - c. Bones and joints
  - d. Chest
  - e. Kidneys
4. Which statement best describes the typical clinical presentation of acute chest syndrome in a patient with sickle cell disease?
  - a. Chest pain and shortness of breath without a fever
  - b. Hypoxia with no other clinical signs
  - c. Shortness of breathe and wheeze
  - d. Fever and bilateral infiltrates on CXR
  - e. Fever, chest pain and lobar infiltrate on CXR
5. Which test is the gold standard for diagnosis of sickle cell disease?
  - a. Haemoglobin electrophoresis
  - b. Gas chromatography
  - c. DNA analysis
  - d. Sickle solubility test
  - e. Peripheral blood film

6. What are the main principles of the perioperative management of a patient with sickle cell disease?
- Oxygenation, hydration, analgesia, avoidance of acidosis, routine preoperative blood transfusion
  - Oxygenation, hyperhydration, analgesia, maintenance of normothermia, avoidance of acidosis
  - Oxygenation, hydration, analgesia, maintenance of normothermia, avoidance of acidosis
  - Oxygenation, hyperhydration, analgesia, maintenance of normothermia
  - Oxygenation, hydration, analgesia, routine preoperative blood transfusion

## INTRODUCTION

Sickle cell disease is a multisystem disease. It is a congenital haemoglobinopathy inherited in an autosomal dominant manner. There are approximately 4 million people worldwide with sickle cell disease. Surgery and anaesthesia carry a high risk for these patients, and meticulous perioperative care is essential to prevent complications of sickle cell disease.

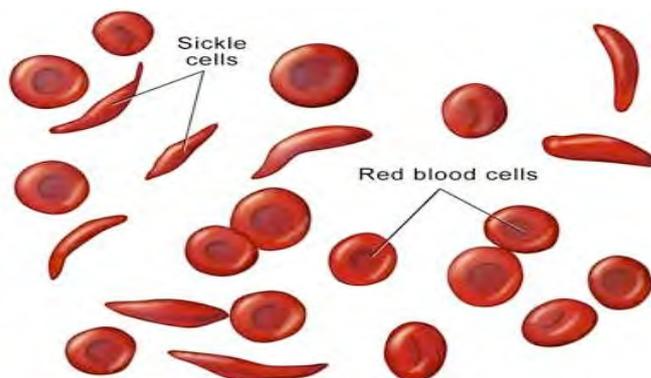
## PATHOPHYSIOLOGY

Adult red blood cells normally contain three different types of haemoglobin. Haemoglobin A (HbA) which makes up 96-98% of total haemoglobin, haemoglobin A2 (HbA2) which accounts for 1.5-3% of the total, and foetal haemoglobin (HbF) which accounts for 0.5-0.08% of the total.

Haemoglobin S (HbS) occurs as a result of a single DNA base change (adenine to thymidine) that results in the substitution of valine for glutamic acid in the  $\beta$ -globin chain.

Sickle cell diseases are inherited in an autosomal co-dominant way, with the homozygous expression of the abnormal gene (HbSS) producing sickle cell disease. These patients have no normal adult haemoglobin (HbA) and only have HbS, HbA2 and HbF, with approximately 95% haemoglobin as HbS. Patients who are heterozygous for HbS (sickle cell trait) are carriers but are asymptomatic and have a normal life expectancy.

Sickle haemoglobin (HbS) polymerises into insoluble microfibrils in the deoxygenated state. It is thought that these parallel microfibrils cause red cell membrane damage and result in the classical sickle cell deformity. The deformed red cells are more rigid and less capable of passing through the microcirculation, causing increased blood viscosity and impaired blood flow. The cells also have a shortened survival time (5-15 days in homozygous sickle cell disease) hence the resulting haemolytic anaemia that is characteristic of sickle cell disease.



**Figure 1:** Normal and sickle red cell morphology

There is increasing evidence that the primary event in sickle disease is oxidative damage to the arterial endothelium (the lining of the vessel wall) due to the effects of sickle haemoglobin breakdown. HbS is extremely unstable and this may be the cause of vascular damage rather than its insolubility. Biochemical markers of endothelial damage are present in sickle cell disease and suggest that perhaps the disease should be considered a chronic inflammatory disorder.

The spectrum of sickling disorders is widened by the combination of HbS with other haemoglobinopathies such as thalassaemia and haemoglobin C and haemoglobin D. This is because polymerisation of HbS is affected by the presence of other haemoglobins, but in varying degrees. For example, patients with HbSD are severely affected, while patients with HbSC are less affected by sickling, and suffer more thrombotic complications. The combination of  $\alpha$  and  $\beta$  thalassaemia with HbS result in disease ranging in severity depending on the nature of the thalassaemia mutation.

## EPIDEMIOLOGY

There are approximately 4 million people with sickle cell disease worldwide. It is most common in West African and Caribbean populations. In Equatorial Africa the sickle cell trait occurs in up to 30% of the population. The high prevalence is a result of balanced polymorphism driven by the relative resistance of heterozygotes to malaria.

In North America approximately 8% of the black population have sickle- cell trait, and up to 1.3% have SCD. The majority of sickle cell disease in the UK is found in African-Caribbean populations in large cities where up to 10% individuals carry the gene.

The HbS gene also occurs in some areas in Mediterranean regions such as Greece, Southern Italy, Turkey, and in Saudi Arabia and Central India.

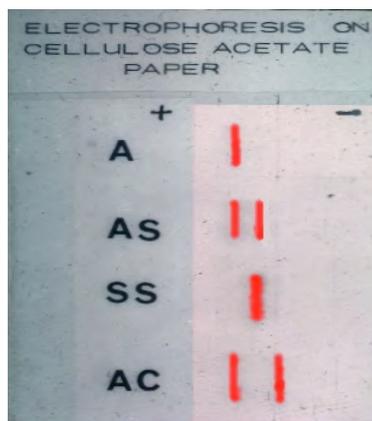
## DIAGNOSIS

The gold standard for diagnosis of sickle cell disease is by haemoglobin electrophoresis.

The simpler Sickledex test confirms the presence of HbS, however electrophoresis is required to distinguish the phenotype. The Sickledex test uses sodium metabisulphite as a reducing agent that causes HbS to precipitate in a hyperosmolar phosphate buffer solution to produce a cloudy suspension.

The Sickledex test is not reliable in the neonatal period as there are low levels of HbS and high levels of HbF that has normal solubility, and may result in a false negative result. It becomes reliable after 6 months of age when the HbF levels have dropped.

Haemoglobin electrophoresis is the only method of distinguishing phenotype. These tests separate molecules on the basis of their charge at a given pH. An example is shown below in Figure 2. Electrophoresis of umbilical cord blood can be used for diagnosis in the newborn.



**Figure 2.** Haemoglobin electrophoresis results for different haemoglobin types.

Antenatal diagnosis of sickle cell disease is possible by analysis of the DNA of foetal tissue from chorionic villous sampling or amniocentesis.

## CLINICAL MANIFESTATIONS OF SICKLE CELL DISEASE IN CHILDREN

Sickle cell disease is a multisystem disorder.

### Anaemia

This is universal in patients with HbSS. Patients usually have a haemoglobin level of 6-9g/dl. The anaemia is usually well tolerated and adequate tissue oxygenation is maintained due to compensatory increase in cardiac output and effective release of oxygen to the tissues due to the low affinity of HbS for oxygen. A systolic flow murmur is a frequent finding and congestive heart failure with cardiomegaly can occur in adults. Children with sickle disease should receive iron and folic acid supplementation.

### Painful crises

This is associated with the sudden onset of severe pain, most commonly arising in bone and joints due to ischaemia and infarction in the marrow or cortical bone. Dactylitis (painful swelling of small bones of hands and feet) occurs in up to half of children by the age of two years and is a sign of severe disease. Abdominal pain occurs in older children and can be caused by bowel dysfunction, organ infarction or referred pain from the ribs. These abdominal crises can present as an 'acute abdomen' and can be difficult to distinguish from acute surgical disorders which cause abdominal pain. One percent of patients have more than six episodes of pain per year. Precipitants for acute painful crises include infection, dehydration, cold, hypoxia and stress. Up to 57% of episodes have no identifiable precipitant.

### Acute chest syndrome

This is defined as fever more than 38.5°C, respiratory distress or chest pain and the appearance of new lobar infiltration on chest X-ray. Hypoxia is common and ventilatory support is occasionally needed in severe sickle chest crisis. The majority of patients are managed with oxygen therapy, hydration and blood transfusion. The incidence of acute chest syndrome in the postoperative child may be as high as 10% in those with severe disease undergoing major surgery. Risk factors for sickle chest crisis are age between 2-4 years and a persistently raised white cell count; these risk factors should be assessed preoperatively. Multiple episodes of acute chest syndrome in children are likely to result in pulmonary fibrosis and chronic lung disease as the child gets older.

### Cerebrovascular accidents (CVA)

The majority of CVAs in patients with sickle cell disease occur during childhood. 5% of children with sickle cell disease have overt CVAs due to ischaemia or infarction. These are typically caused by vascular lesions in the cerebral vessels and may occur as watershed infarctions during a sickle crisis. Transcranial Doppler ultrasonography can identify children at risk of cerebral infarction and it has been shown that treating patients at risk with regular transfusion programmes significantly reduces the incidence of stroke. Children are also at risk of intracerebral and subarachnoid haemorrhages.

### Aplastic crisis

This is usually precipitated by infection, parvovirus being an important pathogen. There is suppression of erythropoiesis in the bone marrow and a dramatic fall in haemoglobin levels. Early diagnosis and treatment with blood transfusion is essential.

### Acute splenic sequestration

This is a rare complication that is commonest in children under five years of age. Large numbers of red cells are sequestered in the spleen and the haemoglobin level drops precipitously. This may present with acute collapse and shock, and may require resuscitation and blood transfusion. Children who suffer repeat episodes of splenic sequestration may require splenectomy.

More commonly, splenic infarction occurs as a result of repeated sickling episodes, which results in functional hyposplenism. Patients are at increased risk of infections, particularly with encapsulated bacteria such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae B*. All children with homozygous sickle disease should receive prophylactic penicillin V from birth.

### Osteomyelitis

SCD patients are at higher risk for osteomyelitis than the rest of the population. The commonest pathogens are salmonella and staphylococci.

### **Priapism**

Attacks start as young as eight years and is reported by up to 30% of male sufferers of sickle cell disease. It can occur in the postoperative period and treatment includes hydration, exchange transfusion and intercavernous injections of an  $\alpha$ -adrenergic agent.

### **Avascular necrosis**

Intravascular sickling of the red blood cells in the microcirculation of the bone results in intramedullary sludging, stasis, thrombosis, and progressive ischaemia, most often of the femoral head. These patients present with pain in the affected joint. Orthopaedic management may be conservative or require surgery.

### **Long-term complications of SCD in adults**

Gall stones, sickle retinopathy, leg ulcers, chronic renal failure due to renal parenchymal scarring, pulmonary hypertension, chronic lung disease, neurological impairment and chronic bone damage may occur as the result of recurrent sickle cell crises.

## **ANAESTHETIC MANAGEMENT OF CHILDREN WITH SICKLE CELL DISEASE**

### **Pre-operative screening**

All children in a high-risk population or those with a positive family history should be screened for sickle cell disease.

### **Pre-operative assessment and preparation**

Patients with history of chest crisis, stroke, or frequent painful crises, or those with severe obstructive sleep apnoea have a higher risk of perioperative complications. All patients with sickle cell disease require meticulous perioperative care.

Pre-operative assessment should involve a careful review of all systems.

- Multiple episodes of acute chest syndrome may result in reduced lung volumes, pulmonary infarction and pulmonary hypertension with low oxygen saturation. It is important to check the baseline oxygen saturation before surgery.
- Although more commonly seen in adults, cardiomegaly may be seen on chest X-ray, and echocardiography may be indicated to assess cardiac function.
- Careful neurological examination is essential and any pre-existing neurological deficit from previous CVA should be documented.
- Renal and hepatic function should also be assessed for signs of end-organ damage. NB even children with HbAS have a renal concentrating defect and they do not tolerate dehydration.

Surgery for children with sickle disease should be planned carefully and their management should be discussed with the anaesthetic and surgical teams, and if possible, with the paediatricians and haematology teams. If there is any evidence of active infection, elective surgery should be postponed.

Where possible, children with SCD should be scheduled first on the theatre list to avoid prolonged starvation and dehydration. Patients should be encouraged to drink free clear fluids until two hours before surgery.

### *Blood transfusion and SCD*

Preoperative blood transfusion is a controversial area, particularly now that anaesthesia care standards have improved for patients with sickle cell disease, the pathophysiology of the disease is better understood and many of the precipitating factors for sickle crisis in the perioperative period can be avoided (see below). The NHS Blood and Transplant service in the UK is undertaking an international

study at present to assess the benefits of preoperative transfusion versus no transfusion in patients undergoing minor and moderate risk surgery (the TAPS study).

Theoretically, reducing the percentage of HbSS by prophylactic transfusion should prevent complications of sickle cell disease. However, aggressive transfusion regimens are associated with a high incidence of transfusion-associated complications.

Blood transfusion carries the risk of allergic reactions, acute haemolytic reactions and transmission of infection. Repeated blood transfusions can cause alloimmunization (the production of antibodies to red cell antigens). These antibodies can cause severe haemolytic reactions. In resource poor areas where screening for infection and highly specific blood cross matching is limited, the balance of the risks versus the benefits of blood transfusion needs to be carefully considered.

Management plans for transfusion therefore need to be individualised for each patient, taking into account the patient's medical history and type of surgery, in consultation with the anaesthetist, surgeon, paediatrician and haematologist, as well as the patient's family.

Guidelines may vary between hospitals and between regions. Transfusion may be used to increase the haemoglobin level; repeated top-up transfusion will also reduce the %S level in blood. Below are current transfusion guidelines at Great Ormond Street Children's hospital in London.

- Children with no special risk factors having short procedures such as insertion of grommets or minor dental work – no transfusion, provided the haemoglobin is at the normal baseline level (Hb >6g/dl)
- Children with no special risk factors having intermediate risk surgery such as tonsillectomy or laparotomy - top-up transfusion to Hb 9-11g/dl.
- Children who have had a chest crisis, CVA or suffer frequent painful crises, or children undergoing major surgery such as thoracic or neurosurgery – sequential top-ups or exchange transfusion to achieve Hb 9-11g/dl AND HbS level <30%.

It is essential to avoid increased tissue viscosity, so in all circumstances the Hb should not exceed 12g/dL.

- Emergency surgery – patients should be treated the same, but if time does not allow, blood should be crossmatched and ready for surgery. All cases should be discussed with a haematologist if possible.

## **INTRAOPERATIVE MANAGEMENT**

### **Oxygenation**

The primary goal is to maintain good oxygenation during the perioperative period. Perioperative pulse oximetry monitoring is essential. Patients may have impaired oxygen delivery resulting from chronic anaemia or chronic lung damage, and may have a limited reserve during hypoxic episodes. Even short periods of hypoxia must be avoided. Postoperative CPAP or a nasopharyngeal airway may be indicated in those with obstructive sleep apnoea (see below).

### **Dehydration**

Dehydration is poorly tolerated. Dehydration leads to increased tissue viscosity, poor perfusion, acidosis and increased sickling. There is little evidence to support the practice of fluid loading or aggressive hydration, however adequate hydration must be maintained pre, intra- and post-operatively and is an essential part of the management of the patient with sickle cell disease. The patient should be encouraged to drink clear fluids up until 2 hours before surgery, or if this is not possible, to have intravenous fluids during the preoperative fasting period. Intravenous fluids should be used during surgery (Ringers lactate or Hartmann's solution only), and postoperative intravenous fluids should be prescribed until oral intake is re-established (see ATOTW 3)

### **Acidosis**

Avoid acidosis. Acidosis causes increased sickling which in turn increases blood viscosity and impairs tissue perfusion. This will cause the tissues to become more acidotic, cause further sickling and could result in a sickle crisis.

### **Temperature management.**

Avoid hypothermia. Hypothermia causes vasoconstriction, hypoperfusion, increased blood viscosity, and decreased venous oxygen tension which all lead to increased sickling.

### **Vascular stasis**

Avoid vascular stasis by maintaining a good circulating volume, careful positioning, and use of pneumatic compression devices if possible in prolonged surgery.

### **Tourniquets**

The safety of the use of tourniquets in patients with sickle cell disease has not been established and should be considered on an individual basis weighing up the risks and benefits. Tourniquets after exsanguination of the limb may be used safely in patients with sickle cell trait.

### **Cell savers**

The high incidence of sickling in cell savers prevents their use in sickle cell disease.

## **POSTOPERATIVE MANAGEMENT**

### **Oxygen therapy**

Oxygen saturation should be monitored continuously and supplemental oxygen should be given to maintain saturations >92%.

### **Fluid management**

Continue intravenous maintenance fluids until the child is tolerating oral fluids.

### **Postoperative analgesia**

Management of post-operative pain is challenging. Patients with sickle cell disease may have very high perioperative analgesic requirements, and may have tolerance to opioids. A multimodal approach should be used with a combination of opioids where indicated, paracetamol and NSAIDs, and regional anaesthesia when possible.

### **Physiotherapy**

Physiotherapy and early ambulation are important to avoid vascular stasis.

### **Nasopharyngeal airway**

Obstructive sleep apnoea secondary to adenotonsillar hypertrophy is common in children with SCD. Careful attention should be paid to these patients postoperatively to avoid airway obstruction, hypoventilation or hypoxia. A nasopharyngeal airway may be used after tonsillectomy or in those with severe OSA to prevent post-operative airway obstruction and hypoxia. In young children, a tracheal tube (the same size as used for surgery) can be cut to length to form a nasopharyngeal airway. The nasopharyngeal airway should not be too long – the tube should be carefully inserted through the nose so that the tip just protrudes from behind the soft palate (approximately equivalent to the distance from the tip of the nose to the tragus of the ear).

## **POSTOPERATIVE COMPLICATIONS**

Serious post-operative complications usually occur within 48hrs of surgery. They include:

- Painful crisis
- Cerebrovascular accident
- Acute chest syndrome

Patients need to be monitored carefully for early signs of complications.

## Management of sickle complications

The anaesthetic team may be involved in managing the acute complications of sickle cell disease, both when they present post-operatively, and when the patient presents to the hospital with an acute crisis.

The management of all sickle crises includes the same principles of establishing intravenous fluids, oxygen therapy, analgesia, and antibiotics.

Analgesia may require high doses of opiates, as well as the use of regular paracetamol and NSAIDs such as ibuprofen or diclofenac.

Transfusion to an Hb > 10g/dl is important, but over transfusion (>12g/dl) must be avoided. Exchange transfusion to reduce HbS < 20-30% may be indicated in certain situations such as acute chest syndrome or CVA. As a guide, transfusion of 4ml/kg of packed cells raises the haemoglobin concentration by 1g/dl; 8ml/kg of whole blood raises the haemoglobin by 1g/dl.

Ventilatory support (continuous positive airway pressure (CPAP), or intubation and ventilation) may be required for acute chest syndrome. Patients should be carefully monitored for signs of respiratory decompensation.

Acute sequestration crisis is an important cause of death in children with sickle cell disease. Acute hypovolaemia can occur due to pooling of blood in the spleen. Treatment is transfusion of blood and intravenous 0.9% saline for volume replacement.

## CONCLUSION

Anaesthetists need to be aware of the possible serious complications of sickle cell disease in the perioperative period. Management of these patients requires careful preparation, and close attention to those factors that can precipitate a sickle crisis. The basic principles of oxygenation, hydration, analgesia, avoidance of hypothermia and acidosis, and blood transfusion where indicated, are essential in these patients.

## ANSWERS TO SELF-ASSESSMENT QUESTIONS

1. b
2. c
3. c
4. e
5. a
6. c

## FURTHER READING AND REFERENCES

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