Update in Anaesthesia

The anaesthetic management of children with sickle cell disease

Based in part upon Locke, C. Anaesthetic management of sickle cell disease in children. A*naesthesia Tutorial of the Week* 153 (2009).

Tanya Smith and Christie Locke*
*Correspondence email: christielocke@me.com

Summary

Sickle cell disease may cause serious perioperative complications. Management of these patients requires careful preparation, and close attention to those factors that could precipitate a sickle crisis. The basic principles of oxygenation, hydration, analgesia, avoidance of hypothermia and acidosis, and blood transfusion where indicated, are essential.

INTRODUCTION

Sickle cell disease (SCD) is a congenital haemoglobinopathy inherited in an autosomal recessive manner. It is a multisystem disease which affects approximately 4 million people worldwide. Surgery and anaesthesia carry a high risk for these patients, and meticulous perioperative care is essential to prevent complications of SCD.[1]

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 0.5-0.8% 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 ß-globin chain.

Sickle cell diseases are inherited in an autosomal recessive fashion, with homozygous expression of the abnormal gene (HbSS) producing SCD. 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 (HbSA) 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 (Figure 1). 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) with the resulting haemolytic anaemia that is characteristic of SCD.

There is increasing evidence that the primary event in SCD is oxidative damage to the arterial endothelium (the lining of the vessel wall) due to the effects of sickle haemoglobin breakdown. The vascular damage caused by HbS, may be due to its extremely unstable

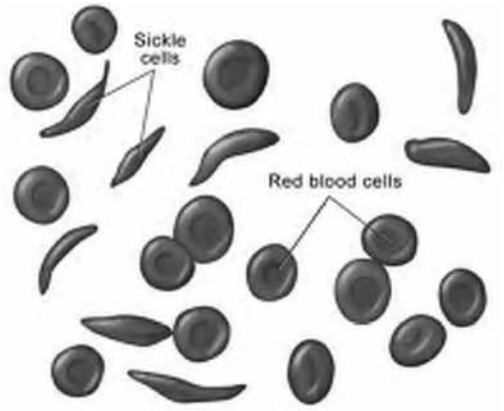

Figure 1. *Normal and sickle red cell morphology*

nature, rather than its insolubility. Biochemical markers of endothelial damage are present and suggest that perhaps the disease should be considered as a chronic inflammatory disorder.

The spectrum of sickling disorders is widened by the combination of HbS with other haemoglobinopathies such as thalaessaemia 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 α and β thalassaemia with HbS result in disease ranging in severity depending on the nature of the thalassaemia mutation.

EPIDEMIOLOGY

SCD affects approximately 4 million people worldwide and 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. This is due to a phenomenon called balanced polymorphism, which is when the heterozygote for two alleles of a gene has an advantage over either of the homozygous states. Heterozygotes for sickle cell anaemia show a marked resistance to malaria. The mechanism for this is unknown but could be explained by the fact that sickle cell trait red cells deform when infected by the

Tanya Smith
Specialist Registrar in Anaesthesia, Northwick Park Hospital, UK

Christie Locke
Consultant Anaesthetist, East Surrey Hospital, UK

parasite, and are then targeted for destruction by phagocytes. The destruction of these cells decreases the parasite burden Because of this relative resistance, people with sickle cell trait in high malaria areas are more likely to reach reproductive age and pass on their genes to the next generation.

In North America approximately 8% of the black population has sickle cell trait, and up to 1.3% has SCD. The majority of SCD 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 the diagnosis of SCD is haemoglobin electrophoresis.

The simpler Sickledex test confirms the presence of HbS, however electrophoresis is required to distinguish between HbSA (sickle cell trait) and HbSS (sickle cell disease).

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 where low levels of HbS and high levels of HbF (with normal solubility) may result in false negative results. It becomes reliable after 6 months of age when the HbF levels have dropped.

Haemoglobin electrophoresis separates molecules on the basis of their charge at a given pH (Figure 2). Electrophoresis of umbilical cord blood can be used for diagnosis in the newborn.

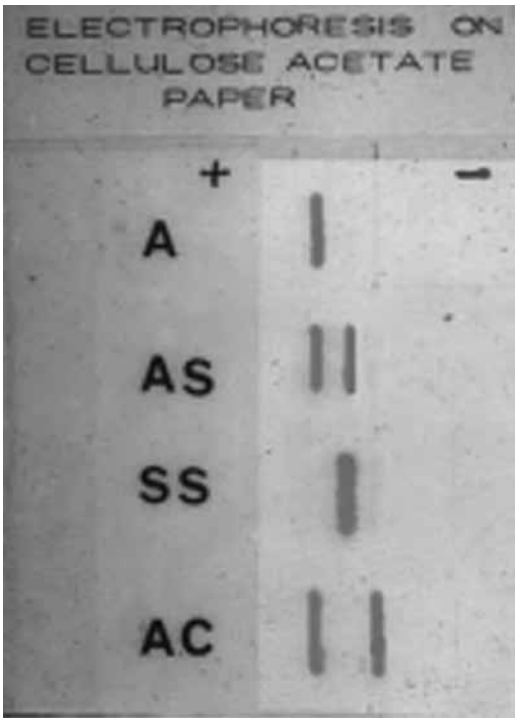

Figure 2. *Haemoglobin electrophoresis results for different haemoglobin types. Antenatal diagnosis of sickle cell disease is possible by analysis of the DNA of foetal tissue from chorionic villous sampling or amniocentesis.*

CLINICAL MANIFESTATIONS OF SCD IN CHILDREN

SCD has a variety of clinical presentations.

Anaemia

This is universal in patients with HbSS. Patients usually have a haemoglobin level of 6-9g.dL^{-1}. The anaemia is usually well tolerated, and adequate tissue oxygenation is maintained due to a compensatory increase in cardiac output and increased effective release of oxygen to the tissues due to the low affinity of HbS for oxygen. A systolic flow murmur (non-pathological murmur as a result of increased cardiac output) is a frequent finding, and congestive heart failure with cardiomegaly on clinical examination/chest radiograph can occur in adults. Children with SCD 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 be difficult to distinguish from other common acute surgical disorders. 1% of patients have more than six episodes of pain per year. Precipitants for acute painful crises include infection, dehydration, cold, hypoxia and stress.

Acute chest syndrome

This is defined as a fever of more than 38.5°C, respiratory distress or chest pain and the appearance of new lung 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. 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 SCD occur during childhood (5% of children with sickle cell disease have overt CVAs due to ischaemia). These are typically caused by vascular lesions in the cerebral vessels and may present as watershed infarctions during a sickle crisis (infarction occurring at the more vulnerable regions between major cerebral arterial zones). Transcranial Doppler ultrasonography can identify children at risk of cerebral infarction, by detecting reduced blood flow in cerebral vessels. 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 haemorrhage.

Aplastic crisis

This is usually precipitated by infection, parvovirus being an important pathogen. There is suppression of erythropoiesis (red blood cell formation) 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 most common in children under the age of five. 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 meningitides, and Haemophilus influenza B*. All children with homozygous SCD should receive prophylactic penicillin V from birth.

Osteomyelitis

Patients are at higher risk of osteomyelitis than the rest of the population, with the most common pathogens being *salmonella* and *staphylococci*.

Priapism

Attacks start as young as the age of eight and are reported by up to 30% of male sufferers of SCD. It can occur in the postoperative period. Treatment includes hydration, exchange transfusion and intra-cavernous 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 surgical.

Long-term complications of SCD in adults

Recurrent sickle cell crises may cause many complications including gall stones, sickle retinopathy, leg ulcers, chronic renal failure due to renal parenchymal scarring, pulmonary hypertension, chronic lung disease, and neurological impairment. Chronic bone damage may occur, leading to avascular necrosis, impaired growth and joint damage.

ANAESTHETIC MANAGEMENT OF CHILDREN WITH SCD

Pre-operative screening

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

Pre-operative assessment and preparation

Patients with a history of chest crisis, stroke, frequent painful crises, or those with severe obstructive sleep apnoea have a higher risk of perioperative complications. All patients with SCD require meticulous perioperative care.[3 4]

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 CVAs should be documented.
- Renal and hepatic function should also be assessed for signs of end-organ damage. Even children with HbAS have a renal concentrating defect and may not tolerate dehydration.
- If there is any evidence of active infection, elective surgery should be postponed.

Where possible, children with SCD should be scheduled first on the operating 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,[5] particularly now that standards of anaesthetic care have improved for patients with SCD. 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 recently undertook a randomized controlled trial to evaluate whether blood transfusion should be given to patients with SCD pre-operatively (so-called TAPS trial). Although the recruitment target was 400 patients, the trial was ended early (after 70 patients) as a review of patient safety identified that there were more serious complications in patients who did not receive pre-operative blood transfusion[6] (unpublished data).

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

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 percentage of HbS in the 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 myringotomy tubes or minor dental work: no transfusion, provided the haemoglobin is at the normal baseline level (Hb >6g.dL^{-1})
- Children with no special risk factors having intermediate risk surgery such as tonsillectomy or laparotomy: top-up transfusion to Hb 9-11g.dL^{-1}

- 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 a Hb of 9-11g.dL^{-1} and a HbS level of <30%
- As it is essential to avoid increased tissue viscosity, the Hb should not exceed 12g.dL^{-1}
- For emergency surgery, patients should ideally be treated the same, but if time does not allow, then 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 as patients may have impaired oxygen delivery resulting from chronic anaemia or chronic lung damage, and may have a limited ability to maintain tissue perfusion and oxygenation during hypoxic episodes. Even short periods of hypoxia must be avoided. Postoperative continuous positive airway pressure (CPAP) or a nasopharyngeal airway may be indicated in those with obstructive sleep apnoea (see below).

Dehydration

Dehydration is poorly tolerated. Dehydration may lead to increased tissue viscosity, poor perfusion, acidosis and increased sickling. Adequate hydration is essential and must be maintained before, during and after surgery. 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, and postoperative intravenous fluids should be prescribed until oral intake is re-established.

Acidosis

Avoid acidosis. Acidosis causes increased sickling, with subsequent increased blood viscosity and impaired tissue perfusion. This will cause the tissues to become more acidotic, causing further sickling, which may 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 the use of thromboembolic deterrent (TED) stockings. Pneumatic calf compression devices can be used during prolonged surgery. These should be avoided if there is evidence of peripheral vascular occlusive disease.

Tourniquets

Studies reporting outcomes after tourniquet use are scarce in patients with sickle cell disease. A recent systematic review concluded that tourniquets may be used with relative safety in most patients, as long as other peri-operative precautions are taken. The use of tourniquets in patients with SCD should therefore be considered on an individual basis weighing up the risks and benefits.

Tourniquet after exsanguination of the limb may be used safely in patients with sickle cell trait.

Cell saver devices

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

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 may have very high perioperative analgesic requirements, and may have developed 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 obstructive sleep apnoea to prevent post-operative airway obstruction and hypoxia.

POSTOPERATIVE COMPLICATIONS

Patients should be monitored carefully for early signs of complications as serious post-operative complications usually occur within 48hrs of surgery. These include:

- Painful crisis
- Cerebrovascular accident
- Acute chest syndrome.

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^{-1} is important, but over transfusion

(>12g.dL^{-1}) 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^{-1} of packed cells or of 8 ml.kg^{-1} of whole blood raises the haemoglobin concentration by 1g.dL^{-1}.

- 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.

CONCLUSIONS

Anaesthetists need to be aware of the possible serious complications of SCD in the perioperative period. Management of these patients requires careful preparation, and close attention to those factors that could precipitate a sickle crisis.[7] The basic principles of oxygenation, hydration, analgesia, avoidance of hypothermia and acidosis, and blood transfusion where indicated, are essential.

REFERENCES

Locke C. Anaesthetic management of sickle cell disease in children. *ATOTW* (2009) **153**. Available at: http://www.wfsahq.org/components/com_virtual_library/media/e0645e0e5cce77faef81cd00f0a0efa4-134dcf42c0b8f21e61db61b943aa0c8b-153-Sickle-cell-disease-in-children.pdf

1. Marchant WA, Walker I. Anaesthetic management of the child with sickle cell disease. Paediatr Anaesth 2003;13:473-89.
2. Nandi R, Martin R. Haematology. In: Bingham R L-TA, Sury M, editor. Hatch and Sumner's Textbook of Paediatric Anaesthesia. 3rd ed, 2008.
3. Firth PG, Head CA. Sickle cell disease and anesthesia. Anesthesiology 2004;101:766-85.
4. Frietsch T, Ewen I, Waschke KF. Anaesthetic care for sickle cell disease. Eur J Anaesthesiol 2001;18:137-50.
5. Hirst C, Williamson L. Preoperative blood transfusions for sickle cell disease. Cochrane Database Syst Rev 2012;1:CD003149.
6. http://www.sicklecellsociety.org/websites/123reg/LinuxPackage22/si/ck/le/sicklecellsociety.org/public_html/news/view/22
7. Davies SC, Oni L. Management of patients with sickle cell disease. BrMed J 1997;315:656-60.