

Review article

Anaesthetic management of the child with sickle cell disease

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Summary

Sickle cell disease (SCD) is a relatively common inherited disorder of haemoglobin with significant morbidity and mortality. This review describes the epidemiology and pathophysiology of the disease, and discusses the clinical manifestations found in children with SCD. A discussion of the evidence concerning the perioperative management of such children is presented.

Keywords: Haemoglobin, Sickle; Anaemia, Sickle cell; Perioperative care; Paediatrics

Introduction

Sickle cell disease (SCD) is part of a heterogeneous group of inherited disorders of the β -haemoglobin chain, characterized by chronic haemolytic anaemia, intermittent vaso-occlusive crises and marked variability in the severity of disease between individuals. It is a multisystem disorder, the acute and chronic manifestations of which are of relevance to the anaesthetist.

Normal adult red blood cells contain three different types of haemoglobin. Haemoglobin A (HbA) is formed by two α and two β globin chains ($\alpha_2\beta_2$), and comprises 96–98% of total haemoglobin. Haemoglobin A₂ (HbA₂) (made up from two α and two δ globin chains, $\alpha_2\delta_2$) accounts for 1.5–3.2%, and fetal haemoglobin (HbF) (made up from two α and two γ globin chains, $\alpha_2\gamma_2$) for 0.5–0.8% (1). Until the first 10 weeks of life, HbF comprises up to 90% of total haemoglobin.

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Haemoglobin S (HbS) contains an abnormal β globin chain because of the inheritance of the sickle β globin gene on chromosome 11. Valine is substituted for glutamic acid in the sixth position of the β globin chain. The mutation appears to be protective against the malaria-causing parasite *Plasmodium falciparum* – red blood cells infected with the parasite appear to sickle easier and are subsequently destroyed by the reticuloendothelial system, protecting the patient from cerebral malaria and death. This protective effect is limited to children with sickle cell trait (2).

SCD occurs in patients homozygous for the HbS gene (SS); normal adult haemoglobin (HbA) is absent and only HbF, HbA₂ and HbS are found. The heterozygous carrier state, sickle-cell trait, is generally harmless and has no effect on life expectancy. Sickle β -thalassaemia, a compound heterozygous syndrome, results from inheritance of the HbS gene, along with a β thalassaemia mutation affecting the other chromosome 11. The severity of this syndrome depends in part upon the nature of the thalassaemia mutation. A β^0 mutation, where no β globin is produced, produces a condition equal in severity to HbSS. Inheritance of a β^+ mutation where

limited production of normal β globin chains occurs, usually leads to a milder phenotype. Sickling disorders may be associated with other abnormal haemoglobins such as haemoglobin C (SC) or haemoglobin D (SD). HbE syndromes are also described, that may lead to severe anaemia with transfusion-dependence (3). α Thalassaemia may also occur in combination with HbS to produce a mild clinical course in childhood, but is thought to lead to increased mortality in adults with sickle disease (4).

Epidemiology

SCD was first recognized in people of West African ancestry. The sickle-cell trait occurs in 10–30% of people in Equatorial Africa but is infrequent in North and South Africa. The HbS gene also occurs around the Mediterranean in Sicily and other parts of Southern Italy, Northern Greece, Turkey, Saudi Arabia and central India (5). DNA studies have identified several populations in whom the HbS mutation arose as a relatively recent event. The sickle mutation may have arisen independently at least five times, which may explain its wide distribution (2).

There are around four million people with SCD globally, of whom some 60 000 are in North America (6). Approximately 8% of the American black population have sickle-cell trait, and 0.3–1.3% have SCD. It is estimated that around 9000 people in London have SCD, making it more common than cystic fibrosis (7). It has been suggested that 250 000 children with SCD are born each year worldwide (5).

Screening for sickle cell disease

Neonatal screening and early diagnosis is essential to prepare preventative and management programs as the greatest mortality in SCD occurs in the first year of life. Without early screening, the mortality from SCD approaches 20% by 3 years of age (8). Major causes of death at this age include pneumococcal sepsis, acute splenic sequestration, aplastic crisis and acute chest syndrome – some of which can be prevented or effectively treated if the underlying diagnosis is known.

SCD can be diagnosed in the newborn period by haemoglobin electrophoresis using umbilical cord blood (9, 10). In the newborn infant with SCD, the haemoglobin electrophoretic pattern is FS (HbF and

HbS), with HbF representing 60–80% of the total haemoglobin. There is no HbA in the neonate. By 3–6 months of age, HbF levels drop to 10–20%, and HbS predominates.

Sickle solubility testing is a simple and quick test to confirm the presence of HbS, although haemoglobin electrophoresis is necessary to distinguish the genotype. The test is based on the precipitation of HbS in a hypermolar phosphate buffer that produces a cloudy suspension within minutes. Those specimens without HbS remain clear. This test for the diagnosis of SCD in the newborn period is not useful as it is too insensitive to consistently detect the low levels of HbS present at birth. In addition, the predominance of HbF (which has a normal solubility) results in negative solubility testing of cord blood in neonates with SCD. False negative results from solubility testing may also be obtained if the total haemoglobin concentration is less than $7 \text{ g}\cdot\text{dL}^{-1}$.

Sickled RBCs may be visible in the peripheral blood smear. However, the inhibitory (and protective) effect of HbF on polymerization of HbS can lead to the absence of sickle cells in the peripheral blood smear in neonates, although mild anaemia would still be seen. This anaemia becomes more marked by the age of about 4 months (11).

Haemoglobin electrophoretic separation techniques are used in more than 40 American states for newborn screening for SCD. However, prematurity, maternal–fetal alloimmunization (such as Rhesus disease of the newborn) and neonatal blood transfusion, have been associated with false-negative results because of dilution of the HbS (12). Table 1 shows the expected results from electrophoresis with the various types of sickle disease. DNA analysis of fetal tissue obtained by chorionic villus sampling (CVS) or amniocentesis allows antenatal diagnosis of SCD late in the first trimester of pregnancy.

The peripheral blood smear in the older child will show irreversibly sickled red cells (up to 30% of total red cells), polychromasia, an occasional nucleated red cell and often small red cell fragments. Absent splenic function is indicated by the presence of Howell–Jolly bodies (nuclear remnants located near the red cell membrane). Target cells are seen in HbSC disease, and moderate to severe hypochromasia is seen in HbS/Thal. The white cell count may be elevated in the absence of infection, and hyper-

Table 1

Results of haemoglobin electrophoresis with various haemoglobinopathies

<i>Diagnosis</i>	<i>Electrophoresis</i>
HbSS	80–90% S 2–20% F <3.6% A ₂
HbSC	45–55% S 45–55% C 2–8% F
HbS/β ⁰ Thal	50–85% S 2–30% F >3.6% A ₂
HbS/β ⁺ Thal	55–75% S 15–30% A 1–20% F >3.6% A ₂
HbAS	38–45% S 55–60% A 1–3% A ₂

segmented neutrophils suggest folic acid deficiency. Platelet counts are elevated, platelet size is increased and clumps of platelets are frequently seen. The reticulocyte count is relatively stable in any given patient, although it varies among patients. Clotting factor VIII and fibrinogen (as well as fibrin degradation products) are increased and become markedly elevated during crises (13).

The mean corpuscular volume (MCV) is elevated because of the high reticulocyte count, and a low MCV suggests other diagnostic possibilities such as HbS/β⁰Thal, iron-deficiency or α-thalassaemia trait. In sickle-cell trait (HbAS), the reticulocyte count, haematocrit, MCV and red cell morphology are normal.

Pathophysiology of sickle cell disease

Irreversible sickling leads to RBC clumping, endothelial damage, an inflammatory response and the clinical syndromes of sickle cell crisis. The various types of crises are vaso-occlusive (painful), megakaryoblastic, sequestration and haemolytic crises.

Sickling results from deoxygenation of HbS. Prolonged deoxygenation causes polymerization of insoluble HbSS strands, a condition termed gellation (14). The distorted sickled cell is the microscopically visible result of this gellation process. *In vitro* studies have shown that the time lag of onset of gellation is

inversely related to haemoglobin concentration and pH (15). Intracellular gellation makes RBCs markedly less deformable; gradual deoxygenation allows long intracellular aggregates to form (resulting in morphologically identifiable 'sickled cells'), whereas rapid deoxygenation causes less membrane deformation as the strands are dispersed throughout the RBC.

Sickle cell RBCs will begin to sickle at oxygen tensions below 5.3 kPa (40 mmHg), although a period of 2–4 min at that oxygen tension is required for marked cellular distortion (2). These conditions are always present in the tissues but RBCs are only in the venous circulation for 10–15 s and therefore sickling is not a problem under normal physiological conditions. However, sickle polymer can be found even in well-oxygenated SS cells with normal morphology. Areas of vascular stasis are more susceptible to sickling; some cells sickle and return to normal as they traverse venous capillary beds where flow is sluggish and oxygen tensions are low. The process of polymerization can be incomplete and reversible if reoxygenation can occur before significant polymerization has occurred, although repeated sickling and unsickling will cause membrane distortion, oxidative damage and irreversible sickling. The oxidative damage occurs because HbS is an unstable haemoglobin and produces oxygen radicals when exposed to oxidant stress (16). In the steady-state, 30% of RBCs are sickled (17). The mean life span of HbSS RBCs is only 12–17 days, instead of 120 days for normal RBCs.

Fully oxygenated HbSS blood is more viscous than HbAA blood at the same haematocrit, because of reduced RBC deformability and increased serum globulins. Furthermore, the viscosity of HbSS blood increases more rapidly with increasing haematocrit. It has been shown that doubling the haematocrit from 30 to 60% causes the viscosity of fully oxygenated HbSS blood to double, but causes a 50-fold increase in viscosity of deoxygenated HbSS blood (18). Higher viscosity promotes vascular stasis; dehydration is therefore an important risk factor for sickling in the clinical setting. The site of microvascular occlusion is thought to be the precapillary sphincters as these are the narrowest point in the microcirculation (19). Interestingly, it has been found that blood viscosity from mixed heterozygotes (SC) increases with deoxygenation at a rate that

roughly parallels clinical severity, and sickle trait (AS) blood shows no tendency to become more viscous even after 1 h of deoxygenation (20). HbSS blood viscosity is significantly improved by admixture of HbAA cells, and this is the basis for recommendation of preoperative transfusion in some circumstances. However, over transfusion may also precipitate a sickle crisis by increasing haematocrit and hence blood viscosity (14).

It has been found that vascular occlusion also involves abnormal RBC adhesion to endothelial cells. The extent of sickle cell adhesion to the vascular endothelium *in vitro* is directly correlated with the clinical severity of vaso-occlusive phenomena in individual patients (21). Inflammatory mediators interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor (TNF) are released as part of an acute inflammatory response. These mediators cause 'up-regulation' of a variety of cell adhesion molecules (CAMs) on endothelial cells resulting in adhesion of sickled cells to the endothelium (22). Evidence also exists for activation of the coagulation system in SCD (23). Therefore, the acute pain crisis of SCD results from the cumulative effects of HbS polymerization, RBC sickling, sickle cell adhesion to vascular endothelium and fibrin deposition, all acting together to cause microvascular occlusion. The finding of activated endothelial cells (of microvascular origin) in the circulation of patients with SCD is thought to play an important role in the development of painful crises (24).

Clinical manifestations of sickle cell disease

SCD is a multisystem disease (Table 2). SCD patients form a new haematological equilibrium with haemoglobin levels of 6–9 g·dL⁻¹ and reticulocyte counts of 5–15%. The combination of a hyperdynamic circulation and the low oxygen affinity of HbS assures near-normal tissue oxygen delivery. Haemolysis demands significant increases in bone marrow activity, along with increased requirements for folic acid. Folic acid deficiency results in megaloblastic erythropoiesis with a low reticulocyte count, increasing MCV and falling haemoglobin (25). Growth impairment is also a feature, as the growth plates compete with the expanded bone marrow for energy and protein. A subnormal weight develops in the first year of life and persists thereafter.

Table 2
Systemic manifestations of sickle cell disease

Haemolysis	Megaloblastic erythropoiesis Aplastic crisis Clinical jaundice and gallstones, liver dysfunction
Vaso-occlusion	Splenic manifestations Stroke Sickle retinopathy Impaired growth Complications in pregnancy
Skeletal	Painful crisis Dactylitis Bone marrow infarcts Osteomyelitis X-ray evidence of osteoporosis
Cardiopulmonary	Cardiomegaly Acute chest syndrome Pulmonary infarcts
Neurological	Stroke Cranial nerve neuropathies
Genitourinary	Poor urine concentrating ability Renal infarction Haematuria Renal failure Priapism

Haemolytic crises

Haemolytic crises, as a result of accelerated RBC death, occur rarely (2). Aplastic crises cause massive suppression of normal erythropoiesis, with absent reticulocytes and a haemoglobin level which falls by about 1 g·dL⁻¹·day⁻¹. A number of different infections are implicated including parvovirus B19, pneumococci, *Salmonella* species, streptococci and Epstein–Barr virus (26). With prompt diagnosis and transfusion, the outcome of aplastic crises is predictable and benign, with bone marrow activity recovery after 7–10 days being the rule (5).

Splenic sequestration crises

Acute splenic sequestration may occur in the first 5 years of life. Vast numbers of RBCs are sequestered in the child's large spleen leading to a precipitous drop in the haemoglobin level. Haemoglobin levels less than 6 g·dL⁻¹ and drops of 3 g·dL⁻¹ below baseline are considered major and these children may require fluid resuscitation and blood transfusion. Haemoglobin levels greater than 6 g·dL⁻¹ are considered minor. Recommendations are for elective splenectomy in all children older

than 2 years in whom one major or two minor sequestration crises have occurred (2). In chronic hypersplenism a new haematological equilibrium is established with a mean RBC lifespan of 2–4 days and haemoglobin levels of 3–4 g·dL⁻¹. Some cases resolve spontaneously but others require chronic transfusion and splenectomy. Chronic hypersplenism may occur as early as 1 year but is most common between 5 and 10 years, and is unusual after 15 years.

More commonly, auto-infarction of the spleen may result in functional hyposplenism that is usually manifest by the age of 7 years (27). Along with defects of opsonization, phagocytic function and cell-mediated immunity, these patients are at a greatly increased risk of systemic bacterial infection and infections at unusual sites, such as osteomyelitis and splenic abscesses (28). Organisms most likely to cause problems in the hyposplenic individual are *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae* (type b).

Acute pain crises

Acute pain in SCD is thought to be caused by vascular occlusion and, in the case of bone pain, the consequent release of inflammatory mediators that results in raised intramedullary pressure and stimulation of nociceptors.

In early childhood the painful crisis is manifest as dactylitis (hand–foot syndrome), which affects the small bones of the hands and feet. It affects 50% of SS children by the age of 2, is commonly recurrent, and becomes less common after 5 years of age. Premature epiphyseal fusion and permanently shortened, deformed small bones may occur secondary to superimposed infection.

After the age of 2, pain remains the commonest manifestation of SCD, with painful episodes being most frequent from 20 to 40 years. The average rate of painful episodes is 0.8 per patient-year in SCD; however, 1% of these patients have more than six episodes per year, whereas some experience none (29). Risk factors for recurrent painful episodes have been identified. HbSS or HbS/β⁰Thal patients tend to have more pain than those with HbS/β⁺Thal or HbSC. Less painful episodes occur in patients with raised levels of HbF and patients with a lower total haemoglobin – most probably because of lower whole blood viscosity associated with a lower

haematocrit. Greater than three pain episodes per year are an indicator of more severe disease and hence, risk of early death (29). The mechanism of action for acute bone pain crises is hypothesized as a centrally mediated reflex that shunts blood away from the medullary cavity (30). Bone pain is frequently symmetrical and most commonly affects the juxta-articular parts of the long bones, notably the hips, knees, elbows, shoulders, ribs, spine and pelvis.

Precipitants for acute pain crises include intercurrent infections, dehydration, exposure to cold, hypoxia, alcohol intake, stress and menstruation. Pain is more likely to start at night possibly because of nocturnal desaturation or relative dehydration. However, 57% of episodes have no identifiable precipitant (16).

The mainstays of management of the acute painful crisis are rest, warmth, reassurance, analgesia and fluid replacement. The presence of fever should prompt a search for an infective focus (including cultures of blood, urine and sputum), although fever may simply be a consequence of sickling. Other medical complications that masquerade as pain should be excluded, including delayed haemolytic transfusion reactions, appendicitis or other abdominal catastrophe, and evolving stroke. Broad-spectrum antibiotics are commonly recommended as there is a high risk of bacterial infections in these patients. Blood transfusion has a limited place in the management of acute painful crises. Steroids have a restricted role; although steroids decrease the opioid requirement and the mean duration of analgesic treatment, they also lead to an increase in the rate of rebound attacks. This, along with fear of the long-term complications of steroid therapy, has discouraged the use of this treatment strategy (31).

The pain of a sickle cell crisis is probably one of the most severe forms of pain (32), with episodes lasting from a few minutes to weeks. Younger children often suffer with limb pain whilst adolescents find abdominal pain the prominent symptom. Options for analgesia include nonsteroidal anti-inflammatory drugs (NSAIDs), which are particularly helpful for bone pain, and a variety of opioid analgesics. These include intramuscular, subcutaneous and intravenous opioids. Patient-controlled analgesia (PCA) techniques are being used increasingly in the management of pain crises

(33). Extradural analgesia has also been used in the management of acute sickle cell crises with continuous local anaesthetic infusions and a combination of local anaesthetic with fentanyl (34).

A further skeletal complication of SCD is osteomyelitis. It occurs up to 200 times more frequently in SCD patients than in the rest of the population, and up to 29% of patients experience at least one episode of osteomyelitis in their lifetime (35). *Salmonella* infections are the cause of over 50% of osteomyelitis cases in SCD patients, and their association with osteomyelitis is almost exclusive in patients with sickle haemoglobinopathies. *Staphylococci* are the second most common cause.

Cardiopulmonary manifestations of sickle cell disease

Acute chest syndrome

The acute chest syndrome (ACS) is the leading cause of death and hospitalization among patients with SCD, being responsible for up to 25% of sickle-related deaths (29, 36). It is caused by a spectrum of pathology including elements of infection, infarction, pulmonary sequestration and fat embolism (37). Data on more than 3750 SCD patients were collected prospectively in The Cooperative Study of Sickle Cell Disease which looked at the clinical features of ACS (36). There were 1722 ACS episodes in 939 patients. The study found that young children (aged 2–4 years) presented with fever and cough, a negative physical examination and rarely had pain. In contrast, adults were often afebrile and complained of shortness of breath, chills and severe pain. Upper lobe disease was more common in children but adults had multilobe and lower lobe disease. Bacteraemia was documented in 3.5% of episodes but was strongly influenced by age (14% of infants and 1.8% of patients older than 10 years old). ACS was most common in winter with children having the most striking increase. The death rate in children was 1.1% compared with 4.3% in adults.

It has been found that a substantial number of patients with ACS have rib infarcts, and it is thought that the resultant splinting of the chest wall with hypoventilation results in rapidly progressive intrapulmonary vaso-occlusion, hypoxaemia, increasing pulmonary problems and ACS (38). A recent multi-

centre study found that a specific cause of ACS was identified in 38% of all episodes (39). Of the patients who died, the most common causes of death were pulmonary emboli and infectious bronchopneumonia.

There is a strong relationship between ACS and the occurrence of neurological complications. A recent history of a pulmonary event is the non-neurological risk factor that is most highly predictive of stroke (40).

The ACS should be treated as a medical emergency and adequate oxygenation ensured by increased inspired oxygen concentrations, CPAP and mechanical ventilation, if necessary. Blood transfusions improve oxygenation and usually reverse respiratory failure within 1–2 days. An alveolar–arterial oxygen gradient of more than 4 kPa (30 mmHg) on air is a predictor of both clinical severity and the need for blood transfusion (41). Bronchodilators and antibiotics also play an important role in the treatment of ACS and intravenous hydration (avoiding over hydration). Airway hyper-reactivity should be assumed to be present, even if the patient is not wheezing, and treatment with bronchodilators should be initiated. Nitric oxide has also been found to be effective in the treatment of severe ACS (42), and the beneficial role of steroids is being investigated (43).

ACS is frequently missed in the postoperative SCD child. The incidence of ACS in the postoperative child has been found to be as high as 10.2% (44). Risk factors include age 2–4 years, SS sickle disease and a persistently raised white cell count (45). Severe anaemia corresponds with decreased episodes of ACS per patient-year, and as with painful crises, a low HbF concentration indicates added risk.

Progressive pulmonary fibrosis has been detected in children with multiple episodes of acute chest crises (46). Lung function testing in adult SCD patients has shown that the predominant abnormality is the presence of a restrictive lung defect (47). Thin-section computed tomography (CT) imaging demonstrates significant multifocal interstitial lung abnormalities in 41% of SCD patients who had previously experienced one or more ACS episodes. The pattern is most consistent with scarring from episodes of infarction or infection (48). Additional abnormalities include altered diffusion capacity and hypoxaemia. A recent study has shown that the

adult restrictive lung defect is probably preceded by obstructive lung disease in children (49).

Cardiac changes in sickle cell disease

Cardiomegaly is a frequent finding in patients with SCD and may occasionally be the presenting feature (50). Studies have varied in their success in identifying a specific cardiomyopathy (51, 52). The majority of patients with SCD demonstrate some abnormality on cardiovascular examination, although in many cases this appears to reflect the circulatory adjustment to chronic anaemia. Signs reflecting a hyperdynamic circulation are found, including widened pulse pressure, active precordial impulses and a laterally displaced, prominent apex beat. Jugular venous pressure is rarely raised in the absence of cardiac failure, and heart sounds are loud, often with a widely split second sound. Accentuation of the pulmonary component is common but does not seem to correlate with the presence of pulmonary hypertension. Systolic murmurs are very common and may be ejection in type, or less commonly, pansystolic. A third heart sound represents the hyperdynamic state rather than failure. A right ventricular heave may be present even in the absence of cor pulmonale, and diastolic flow murmurs reflect the increased flow across a normal valve. Peripheral oedema, crackles, and hepatomegaly may be present as complications of SCD (as a result of venous stasis, pulmonary disease and cholestasis, respectively).

Congestive heart failure may occur in some children (53). Electrocardiogram (ECG) changes in SCD are common and are mainly nonspecific, although changes such as left ventricular hypertrophy, first-degree heart block and right ventricular hypertrophy are found. In general, it appears that the ECG correlates poorly with clinical state and is of limited help in determining the state of the myocardium, or the presence of ventricular hypertrophy.

The cardiac silhouette, on chest X-ray, in SCD is nearly always enlarged as a response to chronic anaemia. Vascular redistribution is uncommon and suggests cardiac failure if present. Echocardiographic studies in SCD children generally show increased left atrial and ventricular dimensions in systole and an increased end diastolic septal and left ventricular free wall thickness. One study found no abnormalities in the ejection or shortening fractions (54)

although another found decreased ejection fractions in SCD children with dyspnoea on moderate exertion (55).

Intravascular occlusion of coronary vessels is rare in SCD although the pulmonary vascular bed is commonly affected. Serial ECGs show no evidence of ischaemia during sickle cell crisis, and CPK-MB isoenzymes are normal despite raised total CPK. There is evidence to suggest that crises may cumulatively affect left ventricular function over years; patients under 23 years with abnormal systolic echocardiograph parameters have had at least 15 crises whereas those with normal measurements have had fewer (56). The clinical sequelae of cor pulmonale are relatively uncommon. In an autopsy series, 22% of SCD children had right ventricular hypertrophy (52).

Neurological manifestations of sickle cell disease

Cerebrovascular accident (CVA) is a severe complication of SCD that may impair both motor and intellectual function. Clinically overt CVAs affect about 5% of children with SCD (40). In addition, as many as 17% of SCD children may have changes on magnetic resonance imaging (MRI) of the brain suggestive of infarction or ischaemia in the absence of the history of stroke (57). The demonstration of specific neuropsychological deficits in these children suggests that these lesions are of clinical importance. Patients with silent infarcts are more likely to have a clinical history of seizure and a lower painful event rate (58). Lower haemoglobin, increased white cell count, elevated haematocrit and Senegal Haplotype (SEN) β^S globin genotype chain (one of up to 13 variants of the sickle β -globin chain identified to date), are associated with the presence of silent infarcts. There is no relationship between silent infarcts and platelet count, HbF level, reticulocyte count, total bilirubin concentration, blood pressure or presence of α -thalassaemia. The lack of protective effect of HbF against silent infarct is surprising as a high level of HbF is believed to be protective against vaso-occlusive complications of SCD (59). The observation that there are more frequent ischaemic brain lesions in the more anaemic patients, and the location of these lesions, are consistent with a watershed perfusion injury. In contrast, overt

strokes in children with SCD typically are caused by vascular lesions in the major cerebral vessels (60). These lesions can be identified by cerebral angiography.

The noninvasive technique of transcranial Doppler (TCD) ultrasonography has been shown to identify these vascular lesions based on increased flow velocity in affected vessels (61) as blood flow is inversely related to arterial diameter. Identifying children at risk of stroke using TCD allows preventative measures to be undertaken. Adams *et al.* performed a prospective randomized controlled trial that included 130 children identified to be at risk of first stroke on TCD. Children were transfused regularly to maintain an HbS level of less than 30%, or assigned to a standard-care group. The incidence of stroke was significantly reduced in the transfusion group (10 cerebral infarctions and one intracerebral haematoma in the standard-care group, as compared with one infarction in the transfusion group) – a 92% reduction in the risk of stroke ($P < 0.001$). The trial was terminated early and carefully managed transfusion programmes were recommended to reduce the incidence of stroke in those considered at risk (62).

Intracerebral haemorrhage is the second most common cerebrovascular complication in SCD, and subarachnoid haemorrhage (SAH) the least common such complication. In contrast with the general population, SAHs in children with SCD are rarely because of aneurysms and are more likely caused by cerebral endarteritis. Also, SAHs tend to occur at a younger age compared with the general population (63).

Renal problems in sickle cell disease

Urological problems encountered are haematuria, urinary tract infection and priapism (64). Few patients experience significant renal bleeding although the incidence of renal parenchyma scarring is high.

The kidney is extremely vulnerable to sickle vaso-occlusion because of the high metabolic rate of the renal medulla with its relatively low blood flow. Impaired tubular function may occur as a consequence of damage to the vasa recta, limiting the concentration of urine. Thus patients with SCD are particularly prone to clinical dehydration and even

patients with sickle trait have impaired urine-concentrating ability. Progressive glomerular fibrosis can lead to chronic renal failure.

Priapism is believed to occur due to the stagnation of blood within the sinusoids of the corpora cavernosa during a physiological erection reducing RBC deformability and impairing the venous outflow from the corporeal bodies. Prolongation of the erection and pain induced by ischaemia of the corporeal tissues are potential consequences. Thirty-eight percent of SCD patients report previous priapism attacks, with the average age of onset being 19 years; some patients may have an attack as young as 8 years of age (65). Frequency of attacks varies from one to 52 episodes per year. There are no significant differences between the clinical and haematological parameters of the SCD patients who do and who do not experience pain lasting longer than 24 h.

Priapism may occur in the postoperative period (66). Haematological parameters that correlate with a history of priapism include a decreased level of HbF and increased platelet count. There are no reliable data concerning the duration of priapism and the risks of impotence. Conservative measures used in the treatment of priapism include hydration, alkalization, exchange transfusions and intracavernous injections of an α -adrenergic agent. Shunting procedures, when necessary, do not necessarily lead to impotence (65).

Perioperative care of the child with sickle cell disease

General considerations

Identification of the SCD patient likely to have severe complications is of use in the preoperative assessment of this patient group. Miller *et al.* prospectively followed the clinical course of a cohort of 392 children from 3 months to about 10 years of age. Factors associated with severe disease in childhood, by multivariate analysis, were the presence of dactylitis, severe anaemia (haemoglobin less than $7 \text{ g}\cdot\text{dL}^{-1}$) and leucocytosis in the absence of infection, occurring in children less than 2 years of age (67). These factors may also indicate a child at increased risk of perioperative complications, although there have been no studies to support this. Early loss of splenic function, as indicated by an increase in haematocrit, may also be prognostically important.

The Adams study (62) would also suggest that a child with abnormal TCD, not on a transfusion programme, may also be at increased perioperative risk, but again, there are no clinical trials to support this.

Preoperative assessment of the patient with SCD should search for evidence of end-organ damage. Respiratory disease from previous ACS episodes may lead to a decrease in vital capacity, intrapulmonary shunting, pulmonary infarction and pulmonary hypertension. Cardiomegaly may be evident on examination and chest X-ray, and systolic dysfunction seen on echocardiography. A full neurological examination should be performed to elicit any neurological deficit from a previous CVA. Renal impairment may also be seen in these patients, who often have a decreased ability to concentrate urine (14). The presence of hepatic dysfunction of various aetiology is a possibility, including vaso-occlusive damage, post-transfusion hepatitis, or cirrhosis. Evidence of bone marrow suppression should be looked for, secondary to hydroxyurea or bone marrow transplantation. Clinical suspicion of disease of any of the above systems should trigger the appropriate further investigations.

The most important clinical factors involved in red cell sickling that need to be addressed when undertaking the perioperative management of a SCD patient are dehydration, deoxygenation, vascular stasis, low temperature, acidosis and infection. Dehydration is poorly tolerated because of impaired urinary concentrating ability. Perioperative fluid management should include preoperative intravenous hydration during periods of fasting, and postoperative intravenous supplementation until an adequate oral intake is guaranteed. Avoidance of overhydration is important (68). Clearly adequate oxygenation during and after surgery must not be forgotten. Perioperative monitoring of oxygen saturation is essential and should be continued postoperatively. Postoperative chest physiotherapy along with incentive spirometry is effective in preventing pulmonary complications in the presence of chest pain (69). The importance of adequate analgesia, to enable effective physiotherapy and early ambulation must be emphasized.

Vascular stasis should be avoided by maintaining a normal/high cardiac output, a normal circulating volume, and normotension. Careful positioning on

the operating table, with attention to venous drainage and the use of pneumatic compression devices in patients who will have prolonged immobilization are helpful. Keeping the patient warm during the perioperative period is another priority. A patient may become hypothermic in the anaesthetic room whilst lines and any nerve blocks are being performed. Warming devices should be used (warm air mattresses, heating blankets, fluid warmers, keeping the patient covered, etc.), and the patient's core temperature should be monitored. Avoiding acidosis involves attention to cardiovascular parameters and fluid balance. Antibiotic prophylaxis should cover organisms relevant to the particular surgery. Infections should be treated aggressively with care not to allow pyrexial patients to become dehydrated.

The merits of general anaesthesia and regional anaesthesia in SCD have been the subject of debate (70, 71). During regional anaesthesia, redistribution of blood flow may lead to an increase in capillary and venous oxygen tension in the blocked region, whilst compensatory vasoconstriction in nonblocked areas leads to a fall in the venous oxygen tension. In addition, lack of control of ventilation, regional hypoperfusion and venous stasis, all create conditions in which sickling can occur. A well-conducted general anaesthetic may be the safest approach. The Cooperative Study of Sickle Cell Disease was a natural history study following 3765 sickle patients over a 10-year period and analysed the courses and outcome of 1079 surgical procedures performed on 717 patients (72). One of the findings was SCD-related complications (defined as painful crisis, ACS, and CVA) after surgery were more frequent in patients who received regional anaesthesia compared with those who received general anaesthesia ($P = 0.058$). Another study examining the effect of different anaesthetic agents on outcome found that the type of agent used had no impact on postoperative morbidity (73). However, this study was retrospective and only involved 45 patients.

Blood transfusion in sickle cell disease

Blood transfusion is one of the only mainstays of therapy in children with SCD. Although transfusion is used in the prevention or treatment of many of the complications of SCD, it has on occasions been used indiscriminately and with considerable risk to the patient. Other than blood transfusion, there are some

other therapies, including hydroxyurea, bone marrow and cord blood transplantation, and improvements in supportive and preventative care.

The use of chronic transfusion programmes has an undisputed role in prevention of CVA in SCD, as discussed previously (62). Transfusion is also used in the treatment of aplastic episodes with severe anaemia, splenic sequestration and the prevention of painful crises (74).

Blood transfusion is by no means a risk-free therapy. Adverse effects include those of infection (including HIV), a rare event in Northern Europe and the United States, but it remains a major concern for patients in developing countries (75). Parvovirus B19 is the predominant cause of aplastic crisis in patients with SCD, so its transmission is a concern. The prevalence of acute B19 infection in blood donors appears low in Europe but may be higher elsewhere (76).

Patients are particularly prone to alloimmunization to transfused red blood cell antigens – the incidence varies from 8 to 50% in patients with SCD (77). This may partly be the result of ethnic and racial differences between blood donors and SCD recipients. The number of antibodies rises as transfusions per patient increase. The presence of antibodies risks the development of severe delayed haemolytic transfusion reactions. Antigen matching between recipient blood and donated blood decreases the likelihood of alloantibody development (78) and all transfused blood should be fully matched for Rhesus and Kell subgroups. Alloimmunization is a major concern in the management of SCD patients, and is one of the driving factors to decrease perioperative transfusions.

Paradoxically, transfusions may also trigger sickle cell events, including pain crises, stroke, and acute pulmonary deterioration. These are thought in part, to occur because of rise in blood viscosity (79).

Anaesthetists should also be aware of the long-term effects of repeated blood transfusions, such as iron overload. Chronic chelation therapy with intravenous, or subcutaneous desferrioxamine may be necessary. Prolonged infusions are necessary as a result of its short half-life.

Preoperative blood transfusion in sickle cell disease

It is known that perioperative complications in patients with SCD are common, with rates as high

as 50% (29). Perioperative blood transfusion is commonly used to prepare SCD patients for surgery. The optimal transfusion regime required to decrease sickling in patients undergoing surgery is controversial. It is thought that limited dilution of sickle cells is beneficial. Blood flow and viscosity depend on both the total level of haemoglobin and the percentage of HbS. A fixed haematocrit of 30% minimizes the rise in viscosity associated with higher proportions of sickle cells (80).

Griffin *et al.* performed a retrospective study of 54 children undergoing 66 elective surgical procedures without preoperative blood transfusion, and 10 children undergoing 10 elective procedures having received preoperative blood transfusion, over a 16-year period (81). They suggested that preoperative blood transfusions might be unnecessary for children with SCD who undergo general anaesthesia for elective minor surgical procedures, such as herniorrhaphy, dental/oral surgery, ophthalmological surgery and tympanostomy tube placement. This applied to patients who were clinically stable with regard to cardiorespiratory status and near baseline with regards to the degree of anaemia preoperatively (i.e. a total haemoglobin level within $1 \text{ g}\cdot\text{dl}^{-1}$ of their usual level). Patients who had a laparotomy, thoracotomy or tonsillectomy and adenoidectomy were found to be at a more significant risk of developing postoperative complications.

The Cooperative Study of Sickle Cell Disease (72) studied 3765 patients prospectively with a mean follow-up of 5.3 years. A total of 717 patients (19%) had at least one surgical procedure, the most frequent being abdominal surgery for cholecystectomy or splenectomy. Ninety-three percent of patients undergoing abdominal surgery received blood transfusion, and there was no association between preoperative HbA level and complication rates (except reduction in pain crisis). Overall 30-day mortality was 1.1%, with no deaths in patients younger than 14 years old. Perioperative transfusion was associated with a lower rate of SCD-related postoperative complications for patients undergoing low-risk procedures (such as those on eyes, skin, nose, ears, distal extremities, dental, perineal and inguinal region) ($P = 0.006$). Conversely, among SCD patients undergoing moderate-risk procedures (defined as those of the throat, neck, spine, proximal extremities, genitourinary system, and

intra-abdominal areas), no association was found between transfusion and sickle-related postoperative complications.

A multicentre randomized controlled trial by the Preoperative Transfusion in Sickle Cell Disease Study Group compared the outcome of an aggressive or a conservative transfusion regimen preoperatively (82). A total of 551 patients were enrolled over a 5-year period (undergoing a total of 604 operations) and randomly allocated to either the aggressive or conservative transfusion regimen. The aggressive regimen maintained a preoperative haemoglobin of $10 \text{ g}\cdot\text{dL}^{-1}$ ($9\text{--}11 \text{ g}\cdot\text{dL}^{-1}$) and a HbS level of 30% or less. The conservative regimen maintained the haemoglobin at $10 \text{ g}\cdot\text{dL}^{-1}$ ($9\text{--}11 \text{ g}\cdot\text{dL}^{-1}$), regardless of the HbS percentage. The mean preoperative HbS in the conservative group was 59%. The frequency of serious complications was similar in the two groups. However, the rate of alloimmunization was double in the aggressive regimen, compared with the conservative regimen (10% vs. 5%, $P = 0.01$). ACS developed in 10% of both groups. Vichinsky *et al.* concluded that a conservative transfusion regimen was as effective as an aggressive regimen in preventing perioperative complications in patients with SCD, and the conservative approach resulted in half the amount of transfusion-associated complications, principally alloimmunization. The study also found that a higher surgical-risk category was a predictive factor for ACS, as was a history of pulmonary disease.

A 10-year retrospective study from The Duke University Experience (83) suggested that preoperative transfusion therapy in children undergoing major surgical procedures was advantageous. The medical records of 92 children were reviewed. All were transfused to reduce the HbS to less than 30%, over a 3–4-week period, although some had exchange transfusions whilst others had simple transfusions. From the study it was concluded that the benefits of an aggressive transfusion regimen in the perioperative period outweighed the risks. The authors of the study acknowledged the weakness of a retrospective study, and that they were less likely to pick up complications.

A recent review from the Cochrane Library database assessed the relative risks and benefits of preoperative blood transfusion regime in patients with SCD undergoing surgery of any type, in any

setting (84). The inclusion criteria for the review were all randomized or quasi-randomized controlled trials comparing preoperative blood transfusion regimes or no transfusion in patients with SCD undergoing surgery. The only study to meet these criteria was The Preoperative Transfusion in Sickle Cell Disease Study Group trial (82). The reviewers felt that recommendations concerning the optimal use of blood transfusion for subgroups of surgical and patient types cannot be made, and further randomized studies are required.

In conclusion, when considering preoperative transfusion practice, each case should be decided on individual merit. The patient's past medical history, risk factors for complications and the planned surgical procedure should all be taken in to account. Discussion should occur between the paediatrician, haematologist, anaesthetist, surgeon and the child's family. A cross-matched unit of blood should always be available for surgery in case of perioperative complications.

Specific procedures

Adenotonsillectomy

Early functional hyposplenism is associated with hypertrophy of other lymphoid tissue, hence adenotonsillar hypertrophy is common. Tonsillectomy has also been found to reduce the incidence of complications associated with *S. pneumoniae* in SCD patients, because of the harbouring of the organism in tonsillar tissue (85). Obstructive sleep apnoea (OSA) secondary to adenotonsillar hypertrophy is common in children with SCD. The peak incidence of childhood OSA coincides with the peak incidence of painful crisis and stroke in children (86). A retrospective study of 75 patients by Halvorson *et al.* found postoperative complications after adenotonsillectomy are increased if the HbS is greater than 40% and in patients younger than 4 years of age (87). These postoperative complications are increased in the presence of OSA. They recommended that children should be transfused preoperatively for elective tonsillectomy, to an HbS of less than 40%, but acknowledged the study limitations (retrospective and over a 14-year period). Chest problems after adenotonsillectomy are thought to be linked to postoperative pain, hypoventilation, atelectasis and subsequent hypoxia. Aggressive

respiratory therapy, bronchodilators and incentive spirometry help to decrease these pulmonary complications.

The link between OSA and hypoxaemia is not clear, as previous work has shown only the minority of patients with SCD and OSA are hypoxic during sleep. Furthermore, the association between hypoxaemia because of OSA and vaso-occlusive events is not established (88). Kirkham *et al.* (89) followed-up 147 patients over a median period of 6 years, to establish whether nocturnal hypoxaemia could be used as a predictor for adverse neurological events (CVAs, transient ischaemic attacks or seizures). Sixty-five percent of the children underwent overnight pulse oximetry. The study found that those children with a high proportion of their sleep study with saturation readings less than 90% were at significantly increased risk of future CNS events. However, intermittent dips in saturation, or previous adenotonsillectomy had no effect on risk. The relevance of this work to postoperative surgical patients has not been investigated.

The Preoperative Transfusion in Sickle Cell Disease Study Group prospectively looked at 118 SCD patients [a subgroup of those studied by Vichinsky *et al.* (82)] undergoing tonsillectomy and/or adenoidectomy and myringotomy, randomly allocated to receive either an aggressive transfusion regimen or a simple transfusion regimen (90). The subjects ranged in age from 1 to 26 years, the median age was 8.2 years. A history of pulmonary disease was found to be a risk factor for postoperative sickle cell-related events. There was found to be no advantage in aggressive transfusion regimens for SCD patients having adenotonsillectomy compared with a conservative regime.

There is no difference in the nocturnal cardiopulmonary function or haemoglobin saturation between patients with mild and severe SCD (91). Clinical trials are needed to determine whether SCD patients with OSA and adenotonsillar hypertrophy have worsening airway obstruction in the immediate postoperative period and are therefore at increased risk of sickle-related complications postadenotonsillectomy.

Cholecystectomy and splenectomy

Splenectomy is performed for sequestration crises and may be performed in early childhood. Chole-

cystectomy is the most common surgical procedure performed in SCD patients (92). The National Preoperative Transfusion Study (93) followed 364 patients undergoing elective cholecystectomy [a subgroup of those studied by Vichinsky *et al.* (82)], randomized to either aggressive or conservative transfusion regimes. Patients who had been transfused within 3 months before surgery were placed in either a transfusion or nontransfusion group, but were not randomized. Fifty-eight percent of the patients had open cholecystectomies and the remaining 42% had laparoscopic cholecystectomies. It found a high (32%) incidence of sickle cell events if the patients were not transfused preoperatively. Laparoscopic patients had longer anaesthesia when compared with open cholecystectomy patients, but a shorter hospitalization. Complications were similar between the two groups. Recommendations of the study were for a conservative preoperative transfusion regimen, and use of the laparoscopic technique. However, Delatte *et al.* in a retrospective review of 63 episodes of ACS within 2 weeks of surgery, found that laparoscopic surgery did not decrease the risk of developing ACS (44).

Emergency cholecystectomy is associated with a high morbidity and should be avoided if possible. It should be noted that it may be difficult differentiating between sickle cell crisis and acute calculous biliary tract disease in the SCD patient (94).

The operative risks of laparoscopic cholecystectomy are now thought to be acceptable and are outweighed by the risks of complications from gallstones. Some groups now will refer SCD patients for laparoscopic cholecystectomy even before development of biliary tract symptoms, if there is evidence of biliary tract disease on investigation (95). A mean postoperative stay of only 1.6 days after laparoscopic cholecystectomy has been reported (96) although others feel that at least 72 h of hospitalization are necessary (97).

Orthopaedic surgery

Orthopaedic disease affects the majority of SCD patients, of which aseptic necrosis of the hip is most common, occurring in up to 50% of patients (98). Sickle cell-related events have been found to occur in 17% of orthopaedic cases (99). The orthopaedic report of the National Sickle Cell Surgery Study Group supports the use of conservative preoperative

transfusion to bring the haemoglobin concentration to between 9 and 11 g·dl⁻¹.

Tourniquets have been used safely in sickle trait patients (100), although they have also initiated sickle cell crises (101). In patients with SCD, circulatory stasis, hypoxia and acidosis beneath and distal to the tourniquet cuff are ideal conditions for the induction of red cell sickling. Use of arterial tourniquets is controversial in SCD although they have been used without development of sickle cell crises (102). This paper was from Saudi Arabia where SCD is reported to have a relatively benign clinical course because of high levels of HbF, and only included 12 patients with HbSS. Careful exsanguination of the limb before tourniquet inflation, and optimum acid-base balance and oxygenation allowed uneventful procedures with a mean tourniquet time of over 1 h. Another study from Nigeria, of 19 patients with SCD, found the incidence of complications significantly higher in SCD patients than in normal patients after use of an arterial tourniquet (103). Therefore, the risks of precipitating a sickle crisis with a tourniquet during surgery in patients with SCD should be balanced against the benefit of operating in a bloodless field.

Neurosurgery

Subarachnoid haemorrhage occurs in considerably younger patients compared with the general population (63). The optimum management of SCD patients with neurosurgical problems requires consideration of preoperative medications and angiography, transfusion therapy and anaesthetic technique. The first problem is the need for contrast medium. These are able to induce sickling (104) and so minimal dye volumes and concentrations should be used. Traditionally, iodinated contrast media have been relatively contraindicated in SCD because the high osmolality may induce osmotic shrinkage of RBCs, impair flow through microcirculation and precipitate a sickle crisis. Modern day contrast media vary in their osmolality from 290 to 1940 mOsm·kg⁻¹. It has been found that the greater the osmolality of the contrast media, the more the mean cell haemoglobin concentration (MCHC) rises. Isotonic media have little effect on RBC volume and no significant effect on the ability of RBCs to pass through synthetic capillary-size pores. Therefore, it is suggested that it is safer to use isotonic contrast

media in SCD (105). Reducing the HbS to less than 40% before angiography has also been shown to reduce the problems of sickling secondary to contrast medium (106).

Of the drugs that may be used in neurosurgery, barbiturates and steroids have been found to be safe in SCD. Epsilon-aminocaproic acid is generally associated with a higher risk of vaso-occlusive complications, although it has been used safely. Increased serum tonicity can induce sickling and so mannitol and frusemide, used for brain volume reduction, may present an increased risk. Urea is thought to be the osmotic agent of choice because it does not produce sickling when mixed with sickle cell blood *in vitro*. This may be because it crosses the red cell membrane freely, producing no osmotic gradient between the intra- and extracellular spaces (104).

Earlier recommendations are for the HbS to be reduced to less than 30–40%, and the haematocrit maintained over 30% (107). There is no evidence regarding optimal management of these patients undergoing neurosurgical procedures, although Adams *et al.* (62) showed that reducing the HbS to 30% in patients at risk of CVA (with abnormal TCD ultrasonography) greatly reduced the risk of a first stroke. The fluid restriction often imposed on patients undergoing craniotomy may be dangerous in the SCD population, and a spinal catheter or ventriculostomy is a good alternative method to reduce intracranial volume. Other than this, the principles mentioned earlier such as careful positioning and avoidance of hypothermia should be adhered to. Theoretically hypothermia, for its cerebral protective effects, should be avoided in these patients.

Cardiac surgery

The issues relating to the need for contrast media for radiological studies have been mentioned earlier. Open-heart surgery using hypothermic cardiopulmonary bypass clearly creates all the conditions that precipitate sickling. Many different methods have been employed to avoid the potentially lethal complications of SCD. Correction of anaemia prior to surgery, partial exchange transfusion, use of blood prime, avoidance of hypoxia and acidosis, and the avoidance of aortic cross-clamping, hypothermia, cardioplegia and topical cooling have all been recommended for open-heart surgery on these patients. The majority of previously reported cases

requiring cardiopulmonary bypass recommend the use of pre- or intraoperative exchange transfusions to reduce the circulating concentration of HbS (108–111). Interestingly, hypothermic cardiopulmonary bypass has been used in two children (undergoing mitral valve replacement) who did not undergo preoperative or intraoperative exchange transfusions (112). Neither child suffered any adverse events, although the pump prime contained blood along with crystalloid.

Exchange can be carried out either in the preoperative period, or on initiation of cardiopulmonary bypass. Preoperative exchange transfusion allows the level of 2,3-diphosphoglycerate to increase, such that it is optimal for the operative procedure (and so increasing oxygen-carrying capacity). Intraoperative exchange transfusion appears more commonly in the literature. In this technique, the extracorporeal circuit is primed with blood, along with fresh frozen plasma, salt-poor albumin, Ringer's lactate, sodium bicarbonate and heparin. The patient's circulating blood volume is collected in a reservoir at the start of cardiopulmonary bypass. The drained blood is centrifuged in a cell saver, and the plasma, rich in platelets and clotting factors, is retransfused into the patient after discontinuation of cardiopulmonary bypass. The concentrated sickle cells are discarded (109, 110).

The use of hypothermia remains controversial in SCD patients undergoing cardiopulmonary bypass. Hypothermia can cause vasoconstriction and red cell sludging, and can therefore potentially increase capillary transit time and the risk of sickling. For this reason, hypothermia is sometimes avoided (111). The successful use of hypothermia (112) may be explained by evidence that, *in vitro*, hypothermia appears to slow polymerization of HbS and delay the onset of sickling of red cells.

It should not be forgotten in these patients undergoing cardiac surgery, the need for care in avoiding precipitating factors of sickle crises throughout the perioperative period and not just during cardiopulmonary bypass.

Conclusion

SCD is a relatively common multisystem disease with life-threatening complications (such as stroke and ACS), in the perioperative period, and is of great

relevance to the anaesthetist. A structured multidisciplinary approach is of great help in the perioperative management of these children. New treatments are being researched, although fine attention to detail of basic measures such as avoidance of perioperative dehydration, adequate analgesia and active mobilization forms the backbone of the anaesthetist's role in the care of these patients.

The subject of perioperative blood transfusion remains controversial. A large multicentre randomized controlled trial found a conservative transfusion regimen as effective as an aggressive transfusion regimen in preventing perioperative complications (82). However, recommendations concerning the optimal use of blood transfusion for high-risk patients (such as those with abnormal TCD, young children with severe OSA, or pulmonary disease) or major surgery cannot be made, and further randomized studies are required. The risk of alloimmunization from blood transfusion is significant and anaesthetists should be aware of this. These risks can be reduced by the use of phenotypically matched blood. It may be possible to avoid blood transfusion completely in certain categories of surgery although further studies in this area are required.

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