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RESEARCH

Paediatric cardiac anaesthesia in sickle cell disease: a case series

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Sickle cell disease (SCD) is the most common inherited haematological disorder, producing a mutation of the haemoglobin molecule known as haemoglobin S (HbS). The presence of HbS in the erythrocyte makes it prone to sickling — a process that may lead to vaso-occlusive injury, haemolysis and a hypercoagulable state. Sickling is precipitated by dehydration, hypoxia, hypothermia, acidosis and low flow situations. Over time, multi-organ damage develops with significant morbidity and mortality. Paediatric patients with SCD and congenital heart defects may require anaesthesia for corrective cardiac surgery on cardiopulmonary bypass (CPB). During the perioperative period these high-risk patients may suffer significant complications when exposed to the conditions that favour erythrocyte sickling.
This case series details experience of four paediatric patients with SCD who underwent corrective cardiac surgery at Red Cross War Memorial Children's Hospital. The pathophysiology is discussed and the perioperative management of transfusion, cardiopulmonary bypass and temperature regulation is highlighted.

Keywords: anaesthesia, cardiopulmonary bypass, sickle cell anaemia, sickle cell disease, transfusion

Introduction

Patients with sickle cell disease (SCD) presenting for cardiac surgery requiring cardiopulmonary bypass (CPB) pose a unique perioperative challenge when exposed to conditions that can elicit erythrocyte sickling with potentially fatal complications.

Literature on the optimal management of these patients is limited, and most contributions on this topic are retrospective case reports or small series.[1,2] In this case series and discussion, we endeavour to heed the call by Mennes et al: 'To increase the available evidence, every experience with cardiac surgery in sickle cell disease patients should be reported.'[3]

Methods

Following approval from the Departmental Research Committee and the University of Cape Town Research Ethics committee, a retrospective review of data on patients with SCD who underwent cardiac surgery was conducted. A total of four patients were identified between April 2004 and May 2013. Seven cardiac surgical procedures were performed, six requiring CPB. In the decade preceding this review, only one patient with SCD underwent cardiac surgery.

Relevant patient information and clinical parameters were collected from the patient records and analysed.

Anaesthetic management

Perioperative management differed between patients. A description of the management principles for these cases is discussed and pertinent information highlighted.

Patients were prepared and optimised for surgery in the Paediatric Intensive Care Unit (PICU) in collaboration with the surgeons, cardiologists, haematologists and intensivists involved. Regular medication was continued until the day of surgery. Oral intake was stopped four hours prior to surgery and intravenous fluid, calculated according to body weight, was initiated. Sedative premedication was not routinely administered. Red cell transfusion prior to surgery was individualised for each patient.

Anaesthesia was induced with inhalation of a sevoflurane and oxygen mixture and intravenous fentanyl (5–10 mcg/kg) and pancuronium (0.1 mg/kg) was administered. Following tracheal intubation anaesthesia was maintained with 1% isoflurane in oxygen and air. Incremental doses of fentanyl (up to 25 mcg/kg) were given.

Invasive monitoring, arterial line and central venous access, was inserted once the patient was deeply anaesthetised. Prophylactic antibiotics were given prior to surgery and repeated four hourly. Heparin 300–400 units/kg was administered prior to bypass and activated clotting time (ACT) was monitored to achieve a value > 480 seconds.

Arterial blood pressure, central venous pressure, electrocardiogram, saturation with pulse oximetry, and rectal temperature were routinely monitored during and after surgery. Cerebral near-infrared spectroscopy (NIRS) was introduced as routine monitoring for cardiac patients in 2007. Patients were transferred to the ICU intubated, and, to achieve sedation and analgesia, infusions of midazolam and morphine were initiated. Patients were monitored in the ICU and, once haemodynamic, pulmonary and cognitive function was optimised, weaned from ventilation and extubated.

Cardiopulmonary bypass

The bypass circuit was primed with a combination of crystalloid, colloid and red blood cells (RBC) to achieve a haematocrit level of 30%. To the prime solution, 2000 units of heparin, 10 ml of sodium bicarbonate and 4 ml calcium gluconate per unit of blood were added. The prime was oxygenated to > 50 kPa before bypass was initiated and maintained throughout the procedure, while venous oxygen saturation was kept at or above 80%. Patients were cooled to 32–34°C. Arterial pH was kept between 7.34 and 7.44 using α-stat. Full flow was calculated using the

patient's height and weight. Routine cardioplegia at this time was crystalloid St Thomas solution.

Results

All patients in this series were immigrants from central Africa undergoing corrective cardiac surgery for congenital heart disease (CHD). Of the seven procedures performed, two required redo-surgery following breakdown of the ventricular septal defect (VSD) patch. Respiratory complications were limited to one episode of collapsed consolidation of the left lung requiring prolonged ventilation. None of the patients developed acute chest syndrome (ACS). Three cases had coexisting pulmonary hypertension (PHT), and in one case it persisted following surgery. The combination of longstanding severe SCD and CHD made the treatment of PHT particularly complex.

Data on cooling on CPB was incomplete, but interestingly case 4, performed in 2013, was cooled to 34°C, possibly reflecting the trend towards mild hypothermia during CPB in SCD cases.[1,4–7]

A limitation of retrospective data collection from patient folders is that key information is often not available. For instance, it is not clear whether perioperative HbA/HbS concentrations were monitored, or when erythrocyte transfusions were performed. Cases 1 and 4 had preoperative HbS concentrations of 97% and 48% respectively. Both these patients had preoperative exchange transfusions. All patients had intraoperative transfusions at initiation of CPB. All patients were discharged home following surgery, but further outcome data are lacking (see Table 1).

Discussion

Epidemiology

The global number of SCD newborns reached 305 800 in 2010, with sub-Saharan Africa accounting for 79% of the total.[2] The incidence in South Africa remains low, but recent research at Red Cross War Memorial Children's Hospital (RCWMCH) haematology clinic demonstrated a sharp increase (300%). This is likely due to the changing population demographics and immigration from Central African countries where the disease is most prevalent.[8] The global prevalence of SCD is predicted to increase, and, along with improved screening programmes, diagnostic and treatment modalities, more patients with SCD may require cardiac surgery in the future.[9]

Genetics

SCD is the most common monogenic disease in humans and also the most common inherited haematological disorder.[8,10] The affected gene is located on chromosome 11, which codes for the β-globin chain of haemoglobin A (HbA). A single point mutation on this gene results in the β-globin chain losing part of its negative charge, changing the solubility and stability of the haemoglobin (Hb) molecule. The Hb constructed of this mutated β-globin chain (Figure 1) is referred to as haemoglobin S (HbS).[3,11,12]

Inheritance is autosomal recessive. The homozygotic phenotype is known as sickle cell anaemia (SCA) and contains HbS (80-98%) and some HbF. The heterozygous phenotype contains normal HbA (60–65%), HbS (35–40%) and some HbF, and is referred to as sickle cell trait (SCT) (see Figure 2). SCA presents with more frequent symptoms and the disease process may be severe and progressive.[3,10,12,13]

Pathophysiology

In affected individuals erythrocytes may sickle when HbS becomes deoxygenated leading to a conformational change and polymerisation of the haemoglobin molecule. This stiffens and disrupts the erythrocyte's structural integrity ('sickling') making it less pliable and more prone to aggregation, vascular occlusion and haemolysis. The degree of polymerisation and sickling is dependent on two aspects: the duration of deoxygenation and the total HbS concentration. Hypoxia, hypothermia, acidosis and

Table 1: Patient demographics and clinical characteristics

	SCA/SCT Gender	Age	Wt/Ht (kg/cm)	Diagnosis	Procedure	AoX/ CPB time (minutes)	Temp	ICU stay
1	SCT & alpha-thalassemia Male	17 m	9/74	Coarctation of aorta Pulmonary hypertension VSD/PDA For staged repair	Coarctation of aorta repair and PA banding VSD not repaired	16/No bypass	35.9	2 days
		2yr 9 m	14/94	Unrepaired VSD	VSD repair & deband PA	48/70	32	2 days
		2yr 9 m	14/94	Residual VSD leak	Repair VSD patch	42/53	32	8 days
2	SCA Female	2yr 8 m	9.8/94	Tricuspid atresia/ restrictive VSD/ASD/pulmonary hypertension	Modified Blalock–Taussig	–		5 days
3	SCT Male	9 m	9.3/80	VSD /mitral stenosis/ sub-aortic stenosis	VSD repair/ resection supra-mitral ring and sub-aortic stenosis	89/133	31.7	3 days
4	SCA Male	6 m	4.6/63	VSD/pulmonary hypertension	VSD repair	26/47	34	8 days
				Residual leak around VSD patch	Repair VSD patch	30/51	34	5 days

SCA = sickle cell anaemia; SCT = sickle cell trait; Wt = weight; Ht = height; AoX = aortic cross clamp; CPB = cardiopulmonary bypass; VSD = ventricular septal defect; PDA = patent ductus arteriosus; Ao = aorta.

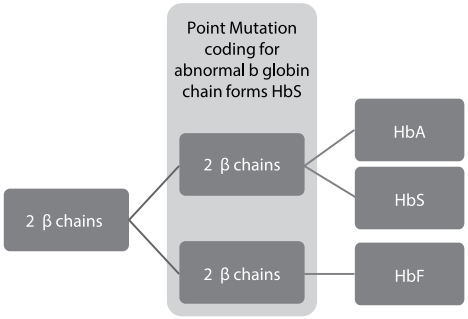

Figure 1: Formation of haemoglobin A, S and F.

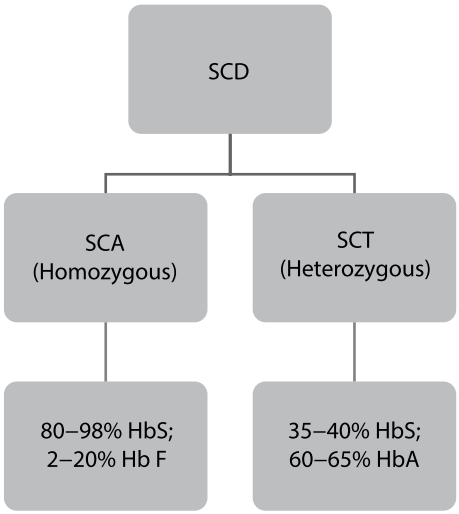

Figure 2: Sickle cell disease genotypes.

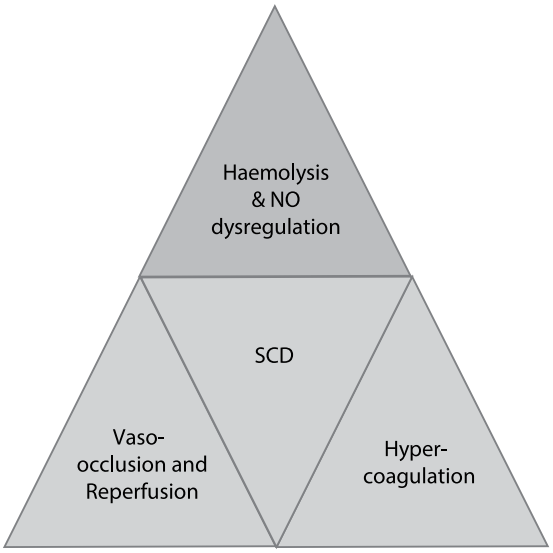

Figure 3: Pathophysiology of sickle cell disease.

low flow states are classically described as triggers for sickling. However, recent research suggests that more complex processes are at play.[3] Once erythrocyte sickling and vascular occlusion occurrs, secondary endothelial inflammation, activation of coagulation and increased expression of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), P-selectin and E-selectin leads to progressive microvascular occlusion. When blood flow to the affected tissues is restored, reperfusion injury occurs with characteristic free radical production, oxidant stress and the release of platelet activating factor (PAF). Repetitive cycles of ischaemia–reperfusion injury lead to multi-organ failure associated with SCD.[10,13,14]

Haemolysis can lead to clinically significant anaemia, but also contributes to endothelial inflammation through the release of Hb and arginase-1 into the plasma.[12] Free plasma Hb scavenges nitric oxide (NO) while arginase-1 metabolises the NO precursor, L-arginase, leading to endothelial dysfunction and worsening microvascular disruption.[3,14]

Dysregulation of coagulation leads to a hypercoagulable state due to activation of platelets, tissue factor and increased platelet numbers[12,15–17] (see Figure 3).

Complications

Over time, ischaemia–reperfusion, haemolysis and hypercoagulability result in a multisystem disease with numerous complications. These are listed with the associated features in Table 2.[10,12,13,15,17–23]

Treatment

Treatment of SCD frequently involves erythrocyte transfusion that increases total Hb concentration, enhances oxygen delivery and improves tissue oxygenation. It also decreases endogenous erythropoiesis, and in this way reduces HbS production. This has been shown to decrease complications associated with SCD, but the risk of acute transfusion reactions and allo-immunisation are increased.[3,12,22–24]

Common indications for transfusion include:

- acute symptomatic anaemia
- aplastic crises
- acute sequestration crises by the spleen or liver
- stroke
- acute chest syndrome (ACS)

Medical management of SCD with hydroxyurea increases HbF concentration and has been shown to decrease the frequency of painful episodes, ACS, the need for blood transfusion, and admission to hospital. Stem cell transplant and gene therapy are reserved for selected cases, usually when other treatment modalities have failed.[12,23]

Perioperative considerations

Preoperative assessment and preparation

A thorough history and examination to evaluate disease severity and the extent of end-organ damage is essential. SCA is more severe than SCT, as is the African haplotype compared with the Asian. Frequency of painful symptoms, ACS and hospital admissions are associated with increased risk of perioperative complications. Intercurrent infection needs to be excluded, as this can trigger sickling events and ACS. Appropriate special investigations should be directed by clinical suspicion of complications and end organ-damage (see Table 2). Recent blood test for Hb level, urea–electrolytes–creatinine, chest X-ray (CXR), and urine dipsticks would be appropriate for most cases.[3,22]

Table 2: Complications of sickle cell disease

Complication	Features
Vaso-occlusive crisis (VOC)	Severe painful episodes associated with vaso-occlusionHigh incidence in: • Homozygous variant • High haematocrit • Low haemoglobin F • Nocturnal hypoxemia • Sibling history of asthma
Pulmonary	
Acute chest syndrome (ACS)	Causes: • Pulmonary infection • Fat embolism • Intravascular pulmonary sequestration of sickled erythrocytesChest X-ray features: • New pulmonary infiltrate, consistent with alveolar consolidation involving at least one complete lung segment
Pulmonary hypertension (PHT)	Major risk factor:Severe haemolytic anaemiaMarkers of haemolysis: • Low steady state haemoglobin • High lactate dehydrogenase • High bilirubin • High reticulocyte countOther causes: • Iron overload • Hepatitis C • Porto-pulmonary hypertension • Thromboembolism • Chronic renal failure • Recurrent ACS
Reactive airway disease	Worsening with ageResults in increased pulmonary artery pressure
Cardiovascular	
Left ventricular (LV) dilation/hypertrophy & diastolic dysfunction	Consequences of chronic anaemia • Increased LV stroke volume, increased cardiac output & heart rate • LV dilatation may develop and progress to LV hypertrophy with decreased LV filling and diastolic dysfunction
Myocardial infarction/dysrhythmias	May develop during vaso-occlusive crisis
Acute right ventricular failure	Secondary to vaso-occlusive crisis or acute chest syndrome
Renal	
Renal impairment	Erythrocyte predisposed to sickling in renal circulation due to: • Low flow state • Low partial pressure oxygen • High oxygen extraction • Low pH • High osmolality leading to cellular dehydration
Recurrent UTI	Common trigger of acute chest syndrome
Neurological	
Cerebrovascular accident (CVA)	Conditions that predispose SCD patients to CVA: • Anaemia • Leucocytosis • Hypoxaemia • Abnormal rheology causing endothelial damage • Functional NO deficiency associated with haemolysis • Impaired regulation of blood flow causing hyperaemia
Subarachnoid and intracranial haemorrhage	– 26% mortality in two weeks
Immunological	
Infection	Prone to infection due to: • Impaired splenic function • Defect in complement activation • Micronutrient deficiency • Tissue ischaemia

Table 2: (*Continued*)

Complication	Features
Auto- or alloimmunisation	Common complication of recurrent erythrocyte transfusions
Haematological	
Acute aplastic crisis	Parvovirus B19 infections trigger acute, severe exacerbations of anaemia
Haemolytic crisis	Acute anaemia often requiring erythrocyte transfusion
Splenic sequestration crisis	Requires elective splenectomy when acute phase resolved
Auto-infarction of spleen	Increased risk of systemic bacterial infection due to: • Defects of opsonisation • Phagocytic dysfunction • Decreased cell-mediated immunity

Special considerations:

- Pulmonary hypertension is increasingly recognised as a perioperative risk factor and poor prognostic indicator.[17,25]
- Hydroxyurea treatment may cause bone marrow suppression. If suspected, discuss with a haematologist.[22]
- Order blood products well in advance. The blood bank needs to perform extended antigen matching.
- Discuss the case with the cardiac surgeon, perfusionists and intensivists and enquire about particular steps, i.e. preoperative transfusion, intraoperative cooling, postoperative plan.
- Inform ICU, determine availability of beds.

Being mindful of the common precipitants of sickling may help in planning the perioperative care of the patient. As a general rule keep the patient warm, well hydrated and comfortable throughout.

Transfusion and cardiopulmonary bypass

Perioperative erythrocyte transfusion has been shown to decrease complications such as ACS, and is accepted practice for all SCD patients undergoing major surgery. A recent randomised controlled trial confirmed these findings, particularly in the SCA patients, although cardiac surgery was excluded in their protocol.[24,26] A transfusion-free cardiac surgery has not been described in SCD as yet and is therefore not recommended.[3]

Whether to transfuse patients pre- or intraoperatively, or what the end points of transfusion should be is not clear.[4] The bulk of the literature reports preoperative transfusion, either as an exchange transfusion or 'top-up' transfusion to adjust Hb levels and HbS concentration. Most often the goal is to achieve a Hb > 10 g/dl and/or HbS < 30%. An increase in adverse transfusion reactions is reported when the latter is targeted.[27] A case series on three paediatric patients with SCD undergoing corrective cardiac surgery describes the use of intraoperative exchange transfusion only at the start of bypass, without any adverse events.[7] The authors concluded: 'We also eliminated the potential harm and distress for the children and their families associated with a preoperative exchange transfusion, which itself carries significant risks without any major reduction in the likelihood of a sickle cell crisis during surgery.'

The patients in our series often required preoperative transfusion to manage the acute disease and not as a prophylactic measure prior to surgery.

The largest case series of 47 SCD patients included 21 paediatric patients who received either preoperative or intraoperative exchange transfusion, or both. Intraoperatively, a haematocrit of 30% and an HbS < 10% was targeted using a combination of RBC, crystalloid and colloid CPB prime, the volume of which was calculated using the patient's age, weight and body surface area (BSA). The prime was oxygenated to > 50 kPa before initiation of CPB and maintained during bypass. Venous oxygen saturation was maintained between 75% and 80%, with a targeted pH of 7.34–7.44. Of these cases, none developed sickling.[1,4] This approach seems to combine the benefits of perioperative transfusion and appropriate CPB set-up effectively to limit the potential for adverse events.

At RCWMCH a similar approach to the one described above was followed.

The principle of perioperative transfusion is to improve oxygen delivery by increasing the HbA concentration, and limit sickling potential by decreasing HbS concentration. Whether a SCD patient is transfused pre-or intraoperatively will depend on his/her current clinical condition and local protocol. The sickling risks are much lower in SCT patients and intraoperative transfusion alone may be a safe option.

Allo-immunisation

Erythrocyte allo-immunisation is the most common transfusion-related complication in SCD patients and may lead to life-threatening haemolytic disease in the foetus and newborn (HDFN), acute haemolytic transfusion reactions (AHTR), and delayed haemolytic transfusion reactions (DHTR). A higher rate of allo-immunisation after multiple transfusions is seen in SCD compared with the general population. This may be due to phenotypic incompatibility between the predominantly black SCD patients and the predominantly white donors described in European and American literature. Indeed, the incidence in Uganda, Nigeria and Jamaica is much lower, where racial antigenic homogeneity between donors and recipients is greater.[4,27–30]

Recent research showed that extended donor/recipient matching reduces allo-immunisation significantly. A large single-centre study found that specifically matching C, E, D, Kell, Kidd, and Fy-a antigens dramatically decreased the incidence. Subsequently, the Blood Transfusion Service made recommendations to perform extended antigen matching for all SCD patients and to issue the closest phenotypically matched blood available.[31] This process may take longer, and blood

Table 3: Sickle cell disease and cardiac surgery: perioperative considerations in a nutshell

S	Is the patient **S**CT or **S**CA? What is the Hb**S** concentration?
C	What **C**omplications and end-organ damage exist?
D	**D**iscuss the patient with haematologist/surgeons/perfusionist/intensivist
C	**C**ardioplegia — preferably blood cardioplegia/**C**ooling 32–34°C
P	**P**recipitants of sickling: hypoxia/hypothermia/acidosis/low flow conditions/dehydration
B	**B**lood products: extensive cross-matching to decrease risk of allo-immunisation

products should be ordered well in advance to avoid delays in issuing the matched blood products.

Allo-immunisation in a SCD patient is potentially catastrophic and all efforts should be made to minimise the risk. Ordering extended antigen-matched blood products timeously, and administering them appropriately, should be a priority during the perioperative care of the SCD patient. Every effort should be made to avoid a transfusion reaction in a patient with an existing haematological disease such as SCD. It is advisable to involve the haematologist and blood bank prior to surgery.

Cooling and cardioplegia

Theoretically hypothermia predisposes HbS to polymerisation and vasoconstriction which may potentiate sickling and vaso-occlusion. Although the most recent publications report cooling to between 32°C and 34°C without adverse events, hypothermic CPB and deep hypothermic arrest have been used with success in SCD patients. The benefits of cooling during CPB need to be weighed against potential complications of sickling due to hypothermia. To avoid sickling of coronary blood, the use of initial warm crystalloid cardioplegia (26–32°C) to flush out residual erythrocytes, followed by cold cardioplegia solution, is advocated.[3–6]

The concerns of cooling and cardioplegia should be considered on a case-to-case basis, and are best discussed with the cardiothoracic surgeon and perfusionist prior to CPB. Depending on the cardiac lesion, the new technique of mild to moderate hypothermia and the use of blood cardioplegia may benefit SCD patients.

Tranexamic acid

The use of anti-fibrinolytics, such as tranexamic acid, has not been validated for SCD patients requiring cardiac surgery/CPB. Its use is described in this setting in two case series and no adverse effects were reported.[1,3,13]

Postoperative care

The goals of avoiding sickling and limiting triggering conditions are followed into the postoperative care phase. To maintain continuity of care, these aims should be clearly communicated with the ICU staff and surgical team.

Transfusion triggers should be discussed and clearly stated in the postoperative orders. To ensure that extended matching can be done by the blood bank, blood products should be ordered in advance. Close monitoring is essential and if complications occur these may be due to ACS or other complications related to SCD and not necessarily due to the surgery.

Adequate pain management is essential to ensure patient comfort and avoid conditions that may predispose patients to sickling.[3] A combination of opiates and paracetamol is usually sufficient. If pain remains difficult to control postoperatively it may be due to an episode of vaso-occlusive crisis (VOC) or chronic pain related to SCD. Other analgesic modalities may need to be considered.[12]

Table 3 summarises the perioperative considerations with the acronym 'SCD–CPB'.

Conclusion

Over the last decade, major cardiac surgery was performed safely in high-risk SCD patients at RCWMCH. To minimise the potential for erythrocyte sickling and adverse events in these patients, a thorough understanding of the pathophysiology and complications is essential. In each case the implications of erythrocyte transfusion, cardiopulmonary bypass, cardioplegia and cooling require special consideration and discussion with the surgeon, perfusionist and intensive care physician. More research and publications in this field would be invaluable to further improve the perioperative care of these patients.

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