Paediatric Cardiac Anaesthesia in Sickle cell disease: a case series

By

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Declaration of Interest

I, *PJ Janse van Rensburg*, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Contents

Abbreviations

ABG	Arterial blood gas
ACS	Acute chest syndrome
ACT	Activated clotting time
AHTR	Acute haemolytic transfusion reaction
ASD	Atrial septal defect
BNP	Brain natriuretic peptide
CO	Cardiac output
CVA	Cerebrovascular Accident
CPB	Cardiopulmonary bypass
CXR	Chest X-ray
DHTR	Delayed haemolytic transfusion reactions
DRC	Departmental research committee
HDFN	Haemolytic disease in the foetus and new born
Hb	Haemoglobin
HbF	Foetal haemoglobin
HbS	Sickle haemoglobin
Hct	Haematocrit
HR	Heart rate
ICU	Intensive Care Unit
LV	Left ventricle
NIRS	Near infra-red spectroscopy
NO	Nitric Oxide
PAF	Platelet activating factor
PAP	Pulmonary artery pressure
PH	Pulmonary Hypertension
PS	Phosphatydil serine
REC	Research ethics committee
ROS	Reactive oxygen species
RR	Risk Ratio
SCA	Sickle cell anaemia
SCD	Sickle cell disease

SCT	Sickle cell trait
VOC	Vaso-occlusive Crisis
TF	Tissue factor
TLC	Total Lung capacity
TRV	Tricuspid regurgitant jet velocity
UCT	University of Cape Town
XO	Xanthine oxidase

Part A: Research Proposal

1. Background

Haemoglobin is the principal oxygen transporter in human red blood cells. Sickle cell disease (SCD) is a common genetic mutation resulting in the variant Haemoglobin S (HbS). Under certain conditions the HbS undergo a process described as sickling due to polymerization of the haemoglobin molecule, precipitating diffuse cellular injury with a variable clinical presentation and potentially life threatening complications. Two types exist: Sickle cell trait (heterozygous), or Sickle cell disease (homozygous), the latter being the more severe form where the majority of circulating haemoglobin is HbS.[1,2]

The incidence of SCD in South Africa is low, although in Sub-Saharan Africa (SSA) it occurs at its highest frequency. Up to 300 000 babies are born with Sickle cell trait (SCT) annually. Due to immigration from the SSA countries, the occurrence of patients with SCD presenting at facilities in South Africa is on the rise. The Haematology/Oncology Service at Red Cross War Memorial Children's Hospital in Cape Town has seen a 300-400% increase in new patients with SCD between 2001-2010.[3]

These patients may present for a range of surgical procedures, not necessarily related to their underlying disease. Common procedures include adeno-tonsillectomy, splenectomy, orthopaedic procedures, neuro- and cardiac surgery. The peri-operative period poses numerous risks to this already vulnerable patient population. Major surgery, like cardiac surgery, has the highest potential to trigger the sickling process and its associated complications - adversely affecting patient outcome.[1] Employing Cardiopulmonary bypass (CPB) during these procedures adds to the list of potential precipitants.[4]

2. Objective

A 5-month-old baby with SCD recently presented for repair of a Ventricular septal defect (VSD), requiring cardiopulmonary bypass, at Red Cross War Memorial Children's Hospital. The importance of a thorough understanding of the pathophysiology of the disease and the need for careful planning in a multidisciplinary fashion was highlighted during the course of the initial surgery and subsequent redo surgery.

This experience led to a detailed review of the literature on sickle cell disease and cardiac surgery in the paediatric population. Advances in research on the molecular basis of the disease process have sparked a surge of interest in this topic.[1,2,5] A recent case series from Great Ormond Street Children's Hospital in the United Kingdom discussed the management of 3 patients with SCD for correction of congenital cardiac lesions requiring cardiopulmonary bypass.[4] Another case series published in Circulation 2010 involved a total of 21 paediatric patients for various corrective cardiac surgical procedures.[6] Because of the relatively

low incidence of the disease, and highly specialised nature of cardiac surgery, very few large trials exist in this area. Case series continues to prove a valuable resource to gain insight in the management of these cases, especially for patients requiring CPB.[4] Review articles on the implications of SCD and anaesthesia were published in Paediatric Anaesthesia 2003 and Anaesthesiology 2004, which attest to the importance of this topic and the need for a thorough anaesthetic management plan in these high risk cases.[1,2]

3. Protocol

Between 2004 and 2013 four patients with sickle cell haemoglobinopathy (two SCD and two SCT) required cardiac surgery at RCWMCH. Two of these patients required redo-surgery for unrelated reasons, therefore, a total of six anaesthetics/surgeries (6 requiring CPB) were performed.

Retrospective data collection from the files of these patients will be analysed: patient demographics, medical background, type of surgery, pre- and intra-operative management, anaesthetic- surgical- and cardiopulmonary bypass-data, post-operative course, with particular attention to transfusion regimen instituted, occurrence of complications and adverse outcome.

A descriptive review of the current literature will be conducted with the aim to provide recommendations on the optimal management of patients with underlying sickle cell disease requiring cardiac surgery.

Patient details and personal information will not be disclosed. Confidentiality will be maintained during the review of their files and data collection.

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Part B: Literature Review

1. Objective

A critical review of the current literature on sickle cell disease with particular emphasis on the implications for paediatric patients presenting for cardiac surgery requiring cardio-pulmonary bypass will be conducted.

2. Literature review strategy

A literature search on Medline was conducted, using keywords: sickle cell disease, sickle cell anaemia, sickle cell trait, cardiopulmonary bypass, cardiac, anaesthesia and transfusion. Literature between 1995 and 2014 were included. Research in adult and paediatric populations was reviewed with an emphasis on paediatric literature.

3. Review and critical appraisal of literature

In 1910 James B Herrick (Professor Of Medicine, Rush Medical College, 1861–1954) published the first detailed case report and description of sickle cell disease. This followed on an earlier description in 1902 by M. Dresbach of an "elliptical, not circular" red blood corpuscle that was sampled from a student at the Ohio State University histology laboratory. Since then it has been recognised that these "peculiar" red blood cells lead to vaso-occlusion and end organ damage as well as complex interactions with the vascular endothelium dysregulation of Nitric oxide (NO) balance and disruption of coagulation.[1]

3.1 Genetics, Biochemistry and Pathophysiology

Sickle cell disease (SCD) is the most common inherited haematological disorder.[2] A single point mutation on the gene coding for the β-globin chain of Haemoglobin (Hb) on chromosome 11, leads to the inheritance of mutant haemoglobin S (HbS).[3,4] See figure 1.

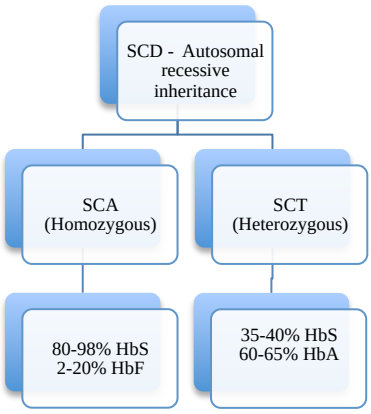

Figure 1: Sickle cell disease genotypes (5) ***Sickle cell disease (SCD) Sickle Cell Anaemia (SCA) Sickle Cell Trait (SCT) Foetal Haemoglobin (HbF) Normal Haemoglobin (HbA)***

The negatively charged, hydrophilic glutamic acid in HbA, is replaced by the neutrally charged non-polar, hydrophobic valine at position 6 on the β-globin chain of Hb to HbS.[6–8] This substation alters its solubility and stability in certain conditions.

Firstly, HbS solubility is decreased when deoxygenated and precipitates out of solution, forming long chains that distort or 'sickle' erythrocytes.

Secondly, the loss of negative charge destabilise the HbS structure leading to accelerated denaturation and breakdown of the molecule, distorting the erythrocyte and predisposing it to haemolysis.[9] Increased vascular inflammation and activation of the coagulation pathways are also involved in the clinical manifestation of SCD, as depicted in figure 2.[4] The clinical conditions required to initiate erythrocyte sickling, such as hypoxia, hypothermia, acidosis and low flow states, are discussed in more detail later.

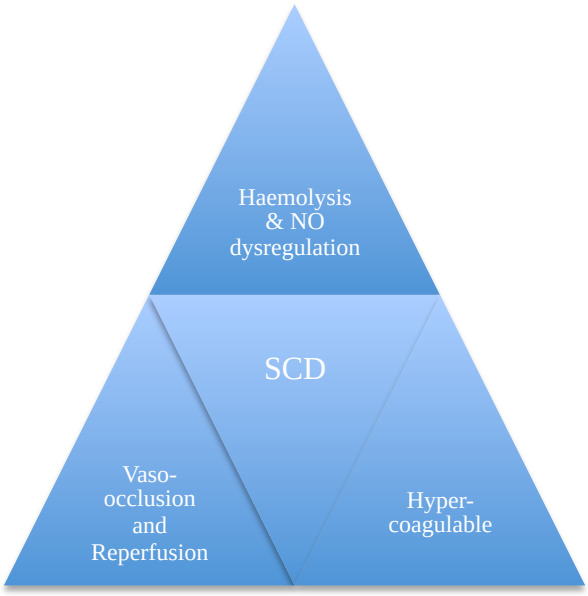

Figure 2: Pathophysiology of sickle cell disease

Vaso-occlusion and reperfusion ischemia injury:

Vaso-occlusive crisis (VOC), or pain crisis is a common manifestation of SCD. HbS polymerisation leads to erythrocyte deformation and rigidity, making them less pliable than normal erythrocytes and prone to vascular and microcirculatory occlusion. Tissue ischemia ensues and upon restoration of blood flow, reperfusion injury occurs. This activates xanthine oxidases (XO) and free radical production, oxidant stress and release of platelet activating factor (PAF). Inflammatory stress and expression of cytokines and endothelial adhesion molecules worsen the cycle of ischemia and reperfusion, potentiating further tissue hypo-perfusion, erythrocyte sickling and endothelial inflammation. In particular adhesion molecules, such as vascular adhesion molccule-1 (VCAM-1), P-selectin (SELP), and E-selectin (SELE), mediate such

interaction responsible for cyclic vaso-occlusion of post-capillary venules, and ischemia-reperfusion injury of multiple organs.[2]

Haemolytic anaemia and Nitric oxide depletion

Polymerisation of HbS and erythrocyte sickling causes haemolysis and clinically significant anaemia.[4] In addition, intravascular haemolysis compartmentalises haemoglobin and arginase-1 realising them into the plasma.

Free plasma Hb generates reactive oxygen species (ROS) such as hydroxyl and superoxide radicals, which actively scavenge Nitric oxide (NO). NO is an essential regulator of vascular function, determining vasodilator tone, especially in the pulmonary vasculature. It also inhibits platelet activation and transcriptional nuclear factor-κB (NF-κB)-dependant expression of adhesion molecules. Due to rapid interaction with haemoglobin, the half-life of NO is exceptionally short, forming methaemoglobin and nitrate. Therefore, free plasma Hb potently inhibits NO signalling leading to NO resistance and endothelial dysfunction.[1,4,10]

Arginase-1 metabolises the precursor of NO generation, L-Arginine, forming ornithine. NO production is subsequently decreased. The amount of NO bound to Hb (S-nitroso-haemoglobin) for transport from the pulmonary circulation to the microvasculature is also decreased, leading to further endothelial dysfunction.[11] The ROS mentioned cause inflammatory damage to the vascular endothelium adding to the dysregulation of endothelial function. Recurrent haemolysis disrupts the regulation of NO availability in this fashion and may lead to Pulmonary Hypertension (PH).[10,12]

Hypercoagulation

A hypercoagulable state and thrombosis is well documented in SCD due to dysregulation of coagulation. In these individuals activation of coagulation pathway depends on multiple triggers and inhibitors to maintain haemostasis. NO is a potent inhibitor of platelet activation, but in SCD chronic NO depletion and arginine deficiency (the substrate for NO synthesis) favours platelet activation. Increased intracellular expression of platelet arginase (arginine consumption) and activation of tissue factor (TF) further potentiates platelet activation and hypercoagulability.[1,13] Recurrent sickling produces sickle erythrocytes with high levels of phosphatydil serine (PS) expression on their membrane surface. With its highly negative charge, PS facilitates the assembly of clotting cascade components and along with increased platelet numbers found in these individuals activation of coagulation is favoured.

3.2 Complications

Due to the pathophysiological changes and challenges SCD patients are exposed to numerous complications of multiple organ systems. The common complications, incidence, clinical consequences and salient features are discussed in Table 3.[1,4,6,13–19]

Table I Complications of sickle cell disease

Complication	*Incidence*	*Clinical Consequence*	*Features*
Vaso-occlusive crisis (VOC)	58-70%	Severe pain with significant morbidity - Lasts minutes to hours - Analgesic control difficult Most common reason for hospital admission. Frequency of admission indicates disease severity.	High incidence in: - Homozygous variant - High Haematocrit - Low Haemoglobin F - Nocturnal hypoxaemia - Sibling history of asthma
Pulmonary			
Acute Chest Syndrome (ACS)	44.8%	Leading cause for: ICU admission Premature death Presentation - Cough - Tachypnoea - Fever - Chest pain - Wheeze	Causes: - Pulmonary infection - Fat embolism - Intravascular pulmonary sequestration of sickled erythrocytes CXR features: New pulmonary infiltrate, consistent with alveolar consolidation involving at least one complete lung segment
Pulmonary Hypertension (PH)	10-20% adults	Develop due to combination of: - Recurrent Haemolytic anaemia - Vasculopathy - NO dysregulation Screening: - Echo: Tricuspid regurgitant velocity - Brain natriuretic peptide levels - Cardiac catheterisation	Major risk factor: Severity of Haemolytic Anaemia Markers of Haemolysis: - Low steady state haemoglobin - High lactate dehydrogenase - High bilirubin - High reticulocyte Other Causes: Iron overload Hepatitis C Porto-PH Thrombo-embolism Chronic renal failure Recurrent ACS
Reactive Airway Disease	53% incidence from birth to 9yr age	Restrictive ventilatory impairment - Mild reduction in Total lung capacity - Reduced diffusion capacity for carbon monoxide	Worsening with age Leads to increased Pulmonary artery pressure in the long term
Cardiac			
Left ventricular (LV) dilation / hypertrophy & Diastolic dysfunction	13%	Diastolic dysfunction - Independent predictor of mortality - Risk ratio of Death: 3.5; with Pulmonary Hypertension: 12.0	Chronic Anaemia cause: - Increased LV stroke volume, increase cardiac output & heart rate - LV dilatation may develop and progress to LV hypertrophy, decreased LV filling and diastolic dysfunction
Arrhythmias	50% Ventricular arrhythmia 38% QT prolongation		Occurs during VOC
Acute right ventricular failure	13%	Acute rise in pulmonary vascular pressure	Due to VOC or ACS

Complication	*Incidence*	*Clinical Consequence*	*Features*
Renal			
Renal impairment	30%	Sickling and vaso-occlusion leading to: Papillary necrosis Medullary fibrosis and Focal segmental glomerulo-sclerosis	Erythrocyte predisposed to sickling in the renal circulation due to: - Low flow state - Low partial pressure and - High oxygen extraction - Low pH - High osmolality leading to cellular dehydration
Recurrent UTI	Common	Haematuria, proteinuria, fever	May trigger ACS
Neurological			
Cerebrovascular accident (CVA)	10%	20% subclinical mental impairment Screening: Transcranial Doppler Treatment: Transfusion to achieve HbS<30% reduce risk by 90%	Predisposed to CVA due to: - 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	2nd & 3rd most common	All ages, most common in 20-30yr old	26% mortality in two weeks
Immunological			
Infection	Common	Infection - *Streptococcus pneumonia* - *Haemophilus influenzae* - non-typhi *Salmonella* Antibiotic prophylaxis and immunisation improve prognosis & outcome	Predisposed to systemic infection due to: - Impaired splenic function - Defect in complement activation - Micronutrient deficiency - Tissue ischaemia
Auto- or alloimmunization	Common	Allo-immunisation Haemolytic transfusion reactions	A consequence of recurrent erythrocyte transfusion
Haematological			
Acute aplastic crisis	Common	Major suppression of Erythropoiesis	Parvovirus B19 infections trigger acute severe exacerbations of anaemia
Haemolytic crisis	Rare	Accelerated erythrocyte breakdown	
Splenic sequestration crisis		Hypersplenism Acute drop in Hb	Elective splenectomy when acute phase resolve
Auto-infarction of spleen	Common	Functional asplenism Result in infections at unusual sites: - Osteomyelitis - Splenic abscesses	Increased risk of systemic bacterial infection due to: - Defects of opsonisation - Phagocytic dysfunction - Decreased cell-mediated immunity

3.3 Treatment

Hydroxyurea combined with regular transfusion and iron chelation are commonly used in the management of SCD patients. Stem cell transplant and gene therapy are used in selected patients.[4] These topics will not be discussed in depth in this literature review.

3.4 General Perioperative considerations

The aim of the preoperative evaluation is to identify risk factors, assess the extent of end organ damage and optimise existing organ dysfunction (Table II). An individualised perioperative management plan is then developed to prevent or limit the potential triggers for sickling. (Table III) [6,19]

Table II SCD patient presenting for surgery – Risk factors and preoperative considerations

Predictors of complications	***Categories / Features***	***Planning / Intervention***
Type of Surgery [20]	Low, moderate or high risk surgery	Right surgery for the right patient
Disease activity and progression of target organ damage [21]	- Frequency of complications - Hospitalisation - Age	Actively seek evidence of target organ damage and investigate with appropriate tests, e.g. CXR for ACS
Progression of Pulmonary complications [6]	- Frequency / clustering of ACS symptoms - Abnormal CXR	- Preoperative physiotherapy - Incentive spirometry - Early ambulation - Adequate pain control (19)
Pre-existing or intercurrent infection [6]	Triggers for ACS	- Treat infection - Appropriate antibiotic prophylaxis - Strict asepsis
Haplotype [6]	More severe disease in African haplotypes	Determine haplotype

Table III Triggers of erythrocyte sickling

Triggers for Sickling	*Considerations*
Deoxygenation No clinical data in the surgical or anaesthetic literature clearly demonstrated hypoxia triggering sickling Complications occurred even if hypoxia was avoided	***Factors affecting oxygen delivery*** Anaemia Obstructive or restrictive lung disease Ventilation-perfusion mismatch Vascular damage Abnormal micro-vascular rheology Peripheral arterio-venous shunting Disturbed NO transport ***Importance of Oxygenation*** Avoidance of anxiolytics, routine hyper-oxygenation or prolonged oxygen supplementation has no proven role over basic perioperative principals of adequate oxygenation and prevention of hypoxia
Dehydration No causal relationship between dehydration and the precipitation of SCD complications In-vitro studies: intracellular dehydration results in increased Hb concentration and sickling	Maintain adequate cellular hydration during perioperative fasting period
Hypothermia Skin chilling triggers VOC	Anaesthesia overrides thermoregulatory mechanisms Actively maintain normothermia
Acidosis Acidosis potentiate erythrocyte sickling during hypoxia	Managing cardiovascular parameters and fluid status to avoid pH imbalances
Vascular Stasis Low flow states, CPB, hypothermia & vasoconstriction	Maintain CO and volume status Positioning, pneumatic compression stockings to aid venous drainage

Erythrocyte transfusion

Erythrocyte transfusion is indicated to 1.) Prevent and treat complications of SCD, 2.) Correct anaemia or 3.) Replace blood loss.

The proposed aims of erythrocyte transfusion in SCD are to increase the haematocrit and reduce the HbS concentration. However, there is no consensus on a safe level of Hb or an ideal proportion of HbA and HbS. The physiological implications of HbS concentrations of 40% are very different in the non-transfused SCT patient, compared to the transfused SCD patient. In SCT, each erythrocyte contains 40% HbS and 60% HbA. In the SCD patient 40% of the erythrocytes contains HbS only and the remaining 60% contains 100% HbA. Each erythrocyte in the SCT patient is more resistant to triggering sickling than the SCD patient. [22]

Controversies around perioperative transfusion in SCD exist and the aims of transfusion in this setting are not clearly defined. The indications for pre-operative transfusion have been difficult to determine conclusively.

In a retrospective observational review of paediatric patients undergoing 66 surgical procedures without preoperative transfusion, Griffin and Buchanan (1993) reported only one episode of ACS and no pain crisis after 46 minor procedures. The authors concluded that the risk of SCD complications is low and the risk of routine transfusion is not justified in minor procedures.[22]

The Cooperative Study of Sickle Cell Disease, a large retrospective review by Koshy et al (1995), reported a reduction in SCD related complications in transfused SCA patients for minor surgery. But this study included adults and children and did not control for confounding variables. They could also not demonstrate any correlation between HbA levels and rate of post-operative complications – except for a decrease in pain crisis in those patients with higher HbA levels. Furthermore the effect of transfusion was dependent on the type of surgical procedure and patient phenotype. Despite inconclusive evidence of benefit they recommended preoperative transfusion to achieve Hb > 10 g/dl without any guidelines to ideal HbS concentration.[21,22]

The Preoperative Transfusion in Sickle Cell Disease Study Group (1995) investigated the impact of different transfusion strategies on outcome variables in SCD requiring surgery. In this multicentre trial SCD patients randomly assigned to receive either an aggressive or conservative transfusion regimen prior to surgery, were compared. Analysis showed comparable complication rates and a doubling of transfusion related complications with the aggressive transfusion regimen.[20] Table IV summarise their findings.

Table IV Complications of pre-operative blood transfusion: Aggressive and Conservative regimen

Transfusion Group	Aims	SCD Complications (ACS/VOC)	Transfusion Complications (Alloimmunisation)
Aggressive	HbS < 30%	31%	14%
Conservative	Hb > 10g/dl	34%	7%

In 1999 the same group published results of 118 patients (adults and children) undergoing elective orthopaedic surgery. Again the perioperative complication rate between the aggressive or conservative transfusion groups did not differ and no advantage could be demonstrated.[23]

Duke University published a 10-year retrospective study (1998) investigating the beneficial effect of preoperative transfusion in major surgery. The transfusion regime was in keeping with the Aggressive transfusion approach of Vichinsky et al, with the aim to reduce the HbS concentration < 30% over 3-4 weeks prior to surgery. The authors recognised the limitations of this retrospective review to pick up complications but recommended to transfuse SCD patients for major surgery preoperatively since the proposed benefits outweigh the risks.[19,24]

A review from the Cochrane Library database in 2001 set out to investigate the relative risks of preoperative transfusion in SCD patients, undergoing any type of surgery in any setting. Only one study met their criteria.(20) Recommendations for subgroups could not be made on the basis of available evidence and need for further randomised studies were expressed.[25]

The Transfusion Alternatives Preoperatively in Sickle Cell Disease study (TAPS), a multi-centre, randomized trial (2013), investigated whether perioperative complications are altered by preoperative transfusion. Groups were randomized to receive no transfusion or preoperative red cell transfusion to achieve Hb concentration > 10g/dl. Patients in the transfusion group who had an Hb < 9g/dl, received a top-up transfusion. Those with Hb > 9g/dl had a partial exchange transfusion to achieve an estimated HbS concentration below 60%. The majority of patients (97%) had SCA. Ten out of the eleven serious adverse events (91%) where ACS, nine of which was in the non-transfused group. The authors concluded that preoperative transfusion of SCA patients undergoing medium risk surgery is beneficial and reduces the risk of perioperative complications.[26]

Although widely practiced, prophylactic preoperative erythrocyte transfusion remains a treatment with significant potential risks and needs to be individualized for each patient in a multi-disciplinary team - surgeon, anaesthesiologist, intensive care physician and haematologist.

3.5 Perioperative considerations for cardiac surgery

The patient with coexisting SCD presenting for cardiac surgery requiring cardiopulmonary bypass creates numerous challenges. High-risk surgery and exposure to a multitude of potential triggers for sickling - low flow states, aortic cross clamping, hypothermia, cold cardioplegia solution and potential for acidosis - requires careful consideration.

Transfusion

The benefit of perioperative transfusion for high-risk surgery was discussed and is accepted practice for patients undergoing cardiac surgery. However, there is no consensus on whether to transfuse pre-operatively or intra-operatively, or what the transfusion targets are. The approach to transfusion varies between institutions and a number of studies and case series/reports describe the safe use of preoperative exchange transfusion or intra-operative exchange transfusion going onto CPB, or a combination of both.[5,9,22,27–29] The latter can be either complete exchange transfusion (whole blood volume is drained from the venous catheter prior to CPB) or partial, which involves separating the whole blood sequestered from the patient into the three components. The erythrocytes are discarded, whilst plasma and platelets are transfused back to patient at the completion of CPB.[22,30]

The potential benefits of exchange transfusion performed with the CPB alone, without preoperative exchange, include reduction in costs, hospital stay, the number of invasive procedures, and exposure to autologous blood units, with no evidence of increased perioperative complication rates.[22] The distress of preoperative transfusion and interventions to patient and family members are also avoided.[29] Yousafzai et al recently published a case series of 47 patients (43 SCA and 4 SCT) undergoing cardiac surgery requiring CPB. Their retrospective review included 21 paediatric patients who received either preoperative or intraoperative exchange transfusion, or both. Intra-operatively 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 patients age, weight and body surface area (BSA). The prime was oxygenated to > 50kPa before initiation of CPB and maintained during bypass. Furthermore, venous oxygen saturation was maintained between 75%-80% and a pH of 7.34-7.44. Of these cases none developed sickling. Reported postoperative complications included exploration for haemorrhage in 3 patients (6.4%), stroke in 2 patients (4.3%), renal failure in 2 patients (4.3%), and prolonged ventilation in 1 patient (2.1%) [9,22]

There are currently no literature on transfusion-free cardiac surgery and cardiopulmonary bypass in SCD patients.

Preparation of blood products

The implications of alloimmunisation are important to consider when preparing a SCD patient for major surgery. Alloimmunisation is the most common complication associated with aggressive preoperative transfusion (to achieve an HbS<30%) and the incidence is twice as high compared to a conservative transfusion protocol (Hb>10g/dl). There is a strong association with the number of units transfused. The reported incidence of alloimmunisation after receiving multiple transfusions is higher in SCD patients when compared to the general population (8-38% vs. 2%).[20] This may be related to the phenotypic incompatibility between the predominantly black SCD patients and the predominantly white donors described in European and American literature. A recent article presented data suggesting significantly lower rates of alloimmunisation (6.1%) amongst a more homogenous Ugandan population of blood donors and SCD recipients.[22,31] It may be that matching blood to race or specific antigens may decrease the patient's susceptibility to alloimmunisation. Additionally, when limited phenotypic matching for the most common erythrocyte antigens (C, E and K) are used the incidence of transfusion related complications decrease.[22,32] A single centre data comparison found that C, E, D, Kell, Kidd, and Fya are the critical antigens to match and dramatically minimized alloimmunisation. The recommendations from this research were recently introduced in the management of SCD patients at RCWMCH.[33] Lastly, it is postulated that a chronic inflammatory state plays a role in developing alloimmunisation, and may contribute to the increased incidence seen in SCD.[32]

Temperature regulation and *Cardioplegia*

Since hypothermia is associated with an increased risk of sickling events the use of hypothermia during CPB in SCD is controversial. Normothermia or mild hypothermia is proposed, though some authors suggest that moderate hypothermia is safe and even deep hypothermic arrest can be employed with success.[9, 22,27,29,34,35]

Another consideration is the use of cold cardioplegia transfused into the coronary vasculature and the risk inducing sickling of RBC and vaso-occlusion. The approaches to limit these events vary with some authors suggesting the use of crystalloid cardioplegia rather than blood cardioplegia to avoid introducing erythrocytes that may sickle into the coronary vessels.[30,36] The temperature of the cardioplegia solution is also debated and some authors advocate an initial transfusion of warm blood or crystalloid cardioplegia, washing out erythrocytes with the potential to sickle, followed by cold cardioplegia.[9,29]

Tranexamic acid

Cardiac surgery requiring CPB and induced hypothermia has the potential to activate the fibrinolytic system. In particular when the blood-artificial surface interaction within the bypass circuit activates thrombin and subsequently lead to initiation of fibrinolysis. This process is not fully suppressed by heparinisation, therefore prophylaxis and treatment of hyperfibrinolysis is important during cardiac surgery involving CPB. The synthetic lysine analogues, tranexamic acid and epsilon-aminocaproic acid, act by reversibly blocking the lysine binding sites of plasminogen, thus preventing its activation to plasmin, and therefore stopping the lysis of polymerised fibrin. It is effective in reducing blood loss, and retrospective data seem to suggest that tranexamic acid might be more beneficial than epsilon-aminocaproic acid.[37,38]

The use of anitfibrinolytics during CPB in SCD patients has not been evaluated but a number of case reports on its use have not shown any detrimental effect.[5,9]

Postoperative Care

There are no literature or guidelines for the post-operative care of SCD following cardiac surgery. Apart from the accepted standard of care, the aims remain avoidance of factors that could potentially provoke erythrocyte sickling - adequate analgesia and avoiding hypoxia, acidosis, hypothermia and dehydration are key to the uneventful management of these patients.

3.6 Conclusion

SCD patients requiring CPB for corrective cardiac surgery is a unique and challenging clinical scenario with numerous anaesthetic considerations. Apart from the impact of surgery, CPB exposes the patient to circumstances that may trigger HbS polymerization and sickling. The aims of perioperative management are to avoid or limit the potential for these conditions to cause complications.

Perioperative transfusion to achieve Hb levels >10 g/dl and HbS concentration < 30% is advocated and this can be achieved pre- or intra-operatively (going onto bypass). High normal CPB flow, mean arterial pressure, and high arterial and venous oxygenation is also commonly employed to maintain perfusion and oxygenation, and prevent acidosis. Mild to moderate hypothermia is acceptable and does not seem to impact on outcome. Extended antigen cross matching dramatically decreases the incidence of alloimmunisation and is essential in SCD who may require multiple transfusions in their lifetime.

A well conducted general anaesthetic in a multidisciplinary team with due consideration of the common complications is essential for optimal patient outcome.

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Part C: Manuscript

Cover Letter

Title Page

Paediatric cardiac anaesthesia in sickle cell disease: a case series

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Keywords: sickle cell disease, pathophysiology, anaesthesia, congenital heart disease, cardiopulmonary bypass, transfusion, tranexamic acid.

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Abstract

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 which may lead to vaso-occlusive injury, haemolysis and a hypercoagulable state. Sickling is precipitated by dehydration, hypoxia, hypothermia, acidosis and low flow states. 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 our experience of four paediatric patients with SCD patients 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: sickle cell disease, pathophysiology, anaesthesia, congenital heart disease, cardiopulmonary bypass, transfusion, tranexamic acid.

Main Text

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. Four patients were identified between April 2004 and May 2013. A total of seven cardiac surgical procedures were performed in these four patients, six procedures 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 optimized 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 individualized for each patient.

Anaesthesia was induced with inhalation of a Sevoflurane and oxygen mixture and after intravenous access was established, Fentanyl (5-10mcg/kg) and Pancuronium (0.1mg/kg) was administered. Following tracheal intubation, anaesthesia was maintained with 1% Isoflurane in oxygen and air. Incremental doses of Fentanyl (up to 25mcg/kg) were given.

Invasive monitoring, arterial line and central venous access, was inserted once the patient was deeply anaesthetized. Prophylactic antibiotics were given prior to surgery and repeated four hourly. Heparin 300-400units/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 was 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 infusions of midazolam and morphine were initiated to achieve sedation and analgesia. Patients were monitored in the ICU and weaned from ventilation and extubated once hemodynamic, pulmonary and cognitive function was optimized.

Cardiopulmonary Bypass

The bypass circuit was primed with a combination of crystalloid, colloid and red blood cells to achieve a haematocrit level of 30%. 2000 units heparin, 10ml of sodium bicarbonate and 4ml calcium gluconate per unit blood were added to the prime solution. The prime was oxygenated to >50kPa before bypass was initiated and maintained throughout the procedure, while venous oxygen saturation was kept at or above 80%. Patients were cooled to between 32 – 34 degrees Celsius. Arterial pH was kept between 7.34 and 7.44. Full flow was calculated using the patient's height and weight. Routine cardioplegia at this time was crystalloid St. Thomas solution.

Results

All patients 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 co-existing pulmonary hypertension (PH). In case 1 symptoms resolved following surgery, but in case 2 it persisted. The PH in the latter possibly developed due to a combination of longstanding severe SCA and not because of the congenital heart lesion alone.

Data on cooling on CPB was incomplete. Of interest case 4, performed in 2013, was cooled to 34°C. This possibly reflects the trend toward mild hypothermia during CPB in SCD cases.[1,4–7]

A limitation of retrospective data collection from patient folders is that key information is not available or was not performed. For instance it is not clear whether perioperative HbA/HbS concentrations was monitored, or when erythrocyte transfusion was performed. Cases 1 and 4 had preoperative HbS concentrations of 97% and 48% respectively. Both these patients had pre-operative exchange transfusions. All patients had intra-operative transfusion at initiation of CPB. See Table I.

Table I Patient demographics and clinical characteristics

	SCA/SCT Gender	Age	Wt/Ht (Kg/cm)	Diagnosis	Procedure	AoX/CPB time(mins)	Temp	ICU stay
1	SCT& alpha-Thalassemia Male	17m	9/74	VSD/PDA/Coarctation of Ao/Pulmonary hypertension	Coarctation of Ao repair and PA banding	16/No bypass	35.9	Ventilate 48hrs
		2yr9m	14/ 94	Residual VSD	VSD Repair / Deband PA	48/70	32	Unknown
	Redo	2yr9m	14/ 94		RedoVSD repair	42/53	32	Unknown
2	SCD Female	2yr8m	9.8/94	Tricuspid atresia/ restrictive VSD/ASD/Pulmonary hypertension	Modified Blalock-Taussig	-		Ventilate48hrs. ICU 5 days
3	SCT Male	9m	9.3/80	VSD / Mitral stenosis / Sub aortic stenosis	VSD Repair / resection Supramitral ring and sub aortic stenosis	89/133	31.7	3 days
4	SCD Male	6m	4.6/63	VSD / Pulmonary Hypertension	VSD repair	26/47	34	8days
					Redo VSD repair	30/51	34	

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

Discussion

Epidemiology

The global number of SCA newborns reached 305 800 in 2010, with Sub-Saharan Africa (SSA) accounting for 79% of the total.[2] The incidence in South Africa (SA) remains low, but recently a sharp increase (300%) was demonstrated in research at Red Cross War Memorial Children's Hospital (RCWMCH). 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 programs, diagnostic and treatment modalities, more patients with SCD may require cardiac surgery in the future.[9]

Genetics

Sickle cell disease (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 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 depicted Hb molecule. The Hb constructed of this mutated β−globin chain (Figure 1) is referred to as haemoglobin S (HbS)[3,11,12]

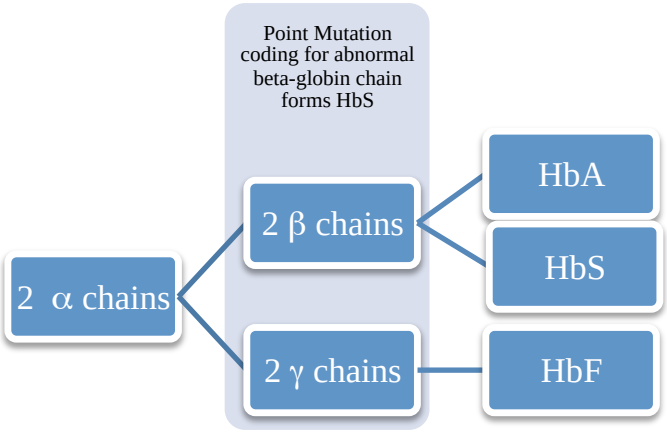

Figure 1 Formation of Haemoglobin A, S and F

Inheritance is autosomal recessive. The homozygous 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 present with more frequent symptoms and the disease process may be severe and progressive.[3,10,12,13]

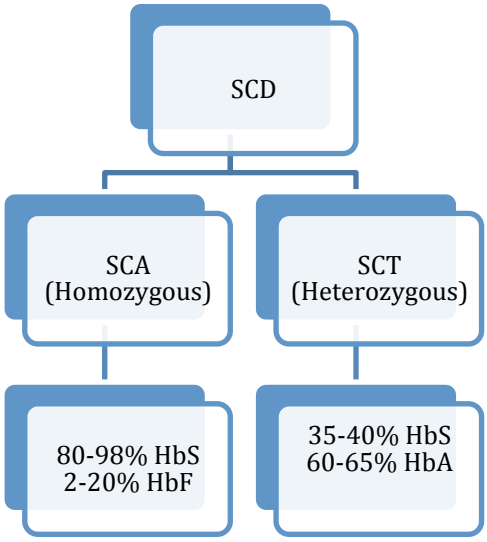

Figure 2 Sickle cell disease genotypes

Pathophysiology

In affected individuals erythrocytes may sickle when the HbS it contains becomes deoxygenated leading to a conformational change and polymerization of the Hb molecule. This stiffens and disrupts the erythrocytes structural integrity ("sickling") making it less pliable and more prone to aggregation, vascular occlusion and haemolysis. The degree of polymerization and sickling is dependent on two aspects: the duration of deoxygenation and the total HbS concentration. Hypoxia, hypothermia, acidosis and low flow states are classically described triggers for sickling. However, recent research suggests that more complex processes are at play.[3]

Following erythrocyte sickling and vascular occlusion, secondary endothelial inflammation, activation of coagulation and increased expression of adhesion molecules such as vascular adhesion molecule-1 (VCAM-1), P-selectin and E-selectin leads to progressive micro-vascular 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 ischemia-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 haemoglobin (Hb) and arginase-1 into the plasma.[12] Free plasma Hb scavenges nitric oxide (NO) while arginase-1 metabolizes the NO precursor, L-arginase, leading to endothelial dysfunction and worsening micro-vascular disruption.[3,14]

Dysregulation of coagulation leads to a hypercoagulable state in SCD. Activation of platelets, tissue factor and increased platelet numbers are some of the aspects involved.[12,15–17] See Figure 3.

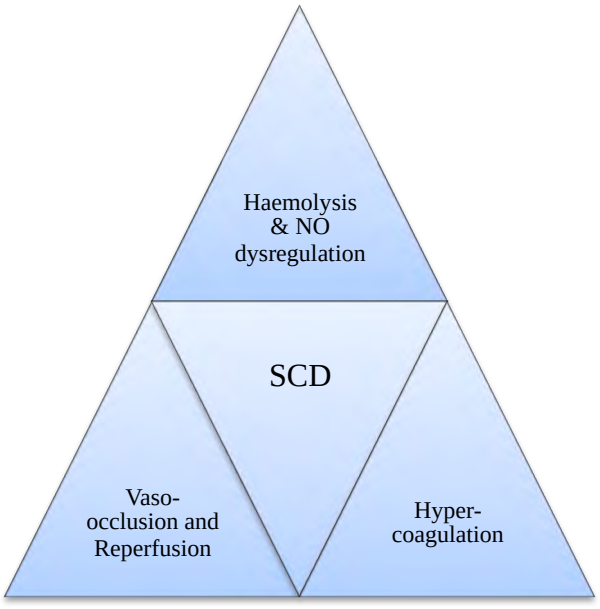

Figure 3 Pathophysiology of sickle cell disease

Complications

Over time, due to the process of ischaemia-reperfusion, haemolysis and hypercoagulability, a multisystem disease develops with numerous complications. These are listed with the associated features in Table II.[10,12,13,15,17–23]

Table II Complications of sickle cell disease

Complication	***Features***
Vaso-occlusive crisis (VOC)	Severe painful episodes associated with vaso-occlusion High incidence in: - Homozygous variant - High Haematocrit - Low Haemoglobin F - Nocturnal hypoxaemia - Sibling history of asthma
Pulmonary	
Acute Chest Syndrome (ACS)	Causes: - Pulmonary infection - Fat embolism - Intravascular pulmonary sequestration of sickled erythrocytes Chest X-ray features: - New pulmonary infiltrate, consistent with alveolar consolidation involving at least one complete lung segment
Pulmonary Hypertension (PH)	Major risk factor: Severe Haemolytic Anaemia Markers of haemolysis: - Low steady state haemoglobin - High lactate dehydrogenase - High bilirubin - High reticulocyte Other Causes: - Iron overload - Hepatitis C - Porto-Pulmonary hypertension - Thrombo-embolism - Chronic renal failure - Recurrent ACS
Reactive Airway Disease	Worsening with age Results in increased pulmonary artery pressure
Cardiovascular	
Left ventricular (LV) dilation/hypertrophy & Diastolic dysfunction	Consequences of chronic anaemia - Increased LV stroke volume, increase cardiac output & heart rate - LV dilatation may develop and progress to LV hypertrophy with decreased LV filling and diastolic dysfunction
Arrhythmias	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

Complication	*Features*
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- & 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
Auto- or alloimmunization	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	Require 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

Treatment

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

Common indications include:

- Acute symptomatic anaemia
- Aplastic crises
- Acute sequestration crises by the spleen or liver
- Stroke
- ACS

Medical management of SCD with hydroxyurea increase HbF concentration and has 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 treatments have failed.[12,23]

Perioperative considerations

Preoperative assessment and preparation

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

Special considerations:

- Pulmonary hypertension is increasingly recognized 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. pre-operative transfusion, intra-operative cooling, post-operative 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 this period.

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 randomized control trial (RCT), 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 intra-operatively, or what the end points of transfusion should be, is not clear.[4] The bulk of the literature reports pre-operative transfusion, either as an exchange transfusion or "top-up" transfusion to adjust Hb levels and HbS concentration.

Most often the goals aimed to achieve a Hb > 10g/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 intra-operative 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 pre-operative 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 pre-operative 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 pre-operative or intraoperative exchange transfusion, or both. Intra-operatively 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 patients age, weight and body surface area (BSA). The prime was oxygenated to > 50kPa before initiation of CPB and maintained during bypass. Venous oxygen saturation was maintained between 75%-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 setup 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 intra-operatively will depend on their current clinical condition and local protocol. The sickling risks are much lower in SCT patients and intra-operative 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 when compared to 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 alloimmunisation 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 provincial 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 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 minimize the risk. Ordering extended antigen-matched blood products timeously, and administering it 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, like SCD. It is advisable to discuss the patient with the haematologist and blood bank prior to surgery.

Cooling and Cardioplegia

Hypothermia, theoretically, predisposes HbS to polymerization and vasoconstriction which may potentiate sickling and vaso-occlusion. Although the most recent publications report cooling to between 32-34°C without adverse events, hypothermic CPB and deep hypothermic arrest have been used with success in SCD patients.[1,4,7,32-34] The benefits of cooling during CPB needs to be weighed against potential complications of sickling due to hypothermia. For the reasons described above, the use of cold cardioplegia solution raises concern. 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 is best discussed with the cardio-thoracic 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]

Post-operative care

The goal to avoid sickling or limit triggering conditions is followed through into the post-operative 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 post-operative orders. Order blood products in advance to ensure that extended matching can be done by blood bank. 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 post-operatively, it may be due to an episode of VOC or chronic pain related to SCD. Other analgesic modalities may need to be considered.[12]

Table III summarises the perioperative considerations. The acronym "SCD-CPB" may be helpful to remember these.

Table III 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 alloimmunisation

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 are 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 is invaluable to further improve the perioperative care of these patients.

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