Interactive CardioVascular and Thoracic Surgery 2022, 35(3), ivac205
https://doi.org/10.1093/icvts/ivac205 Advance Access publication 26 August 2022

ORIGINAL ARTICLE

Cite this article as: Epis F, Chatenoud L, Somaschini A, Bitetti I, Cantarero F, Salvati AC *et al*. Simple open-heart surgery protocol for sickle-cell disease patients: a retrospective cohort study comparing patients undergoing mitral valve surgery. Interact CardioVasc Thorac Surg 2022; doi:10.1093/icvts/ivac205.

Simple open-heart surgery protocol for sickle-cell disease patients: a retrospective cohort study comparing patients undergoing mitral valve surgery

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Received 5 May 2022; received in revised form 22 June 2022; accepted 25 August 2022

Key question

How safe is open-heart surgery for patients suffering from sickle-cell disease in a limited-resource context?

Key finding(s)

In this retrospective cohort study, interventions to control sickling led to comparable morbidity and mortality.

Take-home message

A simple protocol allows sickle-cell disease patients to undergo open-heart surgery with an acceptable risk profile in low-income countries.

Abstract

OBJECTIVES: Sickle-cell disease (SCD) patients are considered to be at high risk from open-heart surgery. This study assessed the role of a simple sickling-prevention protocol.

METHODS: Perioperative non-specific and SCD-specific morbidity and 30-day mortality are investigated in a retrospective cohort study on patients undergoing isolated mitral valve surgery. Patients with and without SCD were compared. In the SCD cohort, a bundle of

interventions was applied to limit the risk of sickling: 'on-demand' transfusions to keep haemoglobin levels of around 7–8 g/dl, cardiopulmonary bypass (CPB) with higher blood flow and perfusion temperature, close monitoring of acid–base balance and oxygenation.

RESULTS: Twenty patients with and 40 patients without SCD were included. At baseline, only preoperative haemoglobin levels differed between cohorts (8.1 vs 11.8 g/dl, $P < 0.001$). Solely SCD patients received preoperative transfusions (45.0%). Intraoperative transfusions were significantly larger in SCD patients during CPB (priming: 300 vs 200 ml; entire length: 600 vs 300 ml and 20 vs 10 ml/kg). SCD patients had higher perfusion temperatures during CPB (34.7 vs 33.0°C, $P = 0.01$) with consequently higher pharyngeal temperature, both during cooling (34.1 vs 32.3°C, $P = 0.02$) and rewarming (36.5 vs 36.2°C, $P = 0.02$). No mortality occurred, and non-SCD-specific complications were comparable between groups, but one SCD patient suffered from perioperative cerebrovascular accident with seizures, and another had evident haemolysis.

CONCLUSIONS: SCD patients may undergo open-heart surgery for mitral valve procedures with an acceptable risk profile. Simple but thoughtful perioperative management, embracing 'on-demand' transfusions and less-aggressive CPB cooling is feasible and probably efficacious.

Keywords: Sickle-cell disease • Cardiac surgery • Rheumatic heart disease • Cardiopulmonary bypass • Transfusions • Sub-Saharan Africa

ABBREVIATIONS

ABG	Arterial blood gas
BSA	Body surface area
CPB	Cardiopulmonary bypass
Hb	Haemoglobin
HbS	Haemoglobin S
ICU	Intensive care unit
NGO	Non-government organization
nSCD	Non-sickle-cell disease
pRBCs	Packed red blood cells
SCD	Sickle-cell disease
SSA	Sub-Saharan Africa

INTRODUCTION

Sickle-cell disease (SCD) affects more than 30 million people worldwide, with a greater incidence in sub-Saharan Africa (SSA), the Mediterranean Basin, the Middle East and India [1]. The autosomal recessive mutation of the β-globin gene leads to an abnormal haemoglobin (Hb), called 'S' (HbS) [2]. Low oxygen tension causes HbS polymerization, responsible for erythrocytes' deformation into an irregular sickle shape. Stiffness in sickle cell walls leads to microvascular occlusion, reperfusion injury, infarction, chronic haemolysis, endothelial dysfunction and inflammatory vasculopathy [1], causing a multi-systemic involvement, with flare-ups, progressive organ damage, lower quality of life and limited life expectancy [2].

During the perioperative period, SCD patients are exposed to a greater risk of vaso-occlusive crisis, acute chest syndrome, congestive cardiac failure, perioperative infections and increased mortality. A careful preoperative evaluation and a thoughtful perioperative management are therefore mandatory [3, 4].

During and after open-heart surgery patients may experience hypothermia, hypoxia, acidosis and low blood flow, all of them recognized as triggers for sickling crisis [5]. Unfortunately, the information coming from previous studies [6–8] is of limited use in managing patients safely.

At the *Salam* Centre for Cardiac Surgery, in Sudan [9], SCD patients with advanced rheumatic heart disease or congenital heart disease are a frequent problem, therefore a simple sickling-prevention protocol with several interventions was set up. The efficacy and safety of this approach were investigated in this study.

MATERIALS AND METHODS

Study design

This retrospective cohort study includes two cohorts of patients, a cohort of patients with SCD (as cases) and a cohort of patients without SCD [non-sickle-cell disease (nSCD), as controls].

Study setting

This study was carried out at the *Salam* Centre for Cardiac Surgery in Khartoum, Sudan, built and ran by the non-government organization (NGO) EMERGENCY in cooperation with the Sudanese government [9].

Data sources and patient enrolment

Patients were identified from the centre's 2010–2019 institutional electronic database. Only rheumatic heart disease patients who had undergone isolated mitral valve surgery were selected, considering both valve replacement with mechanical prosthesis and valve repair. Redo cardiac surgery was excluded.

All patients with a confirmed diagnosis of SCD were enrolled. For each SCD patient (case), a third-party researcher recruited from the same database two patients without SCD diagnosis (nSCD patients, controls) among those who underwent isolated mitral valve surgery and matched (1:2) by gender, age (±2 years) and period of surgery (±6 months), as reported in flow chart (Fig. 1). We verified the absence of a medical history suggestive for SCD in the controls' cohort.

Sickle-cell disease diagnosis

When SCD was reported in the database, the diagnosis was verified by checking the individual patient's medical records, looking for both clinical signs and symptoms of SCD in patients' histories and a positive laboratory test. According to our protocol (Table 1), patients presenting with severe anaemia (Hb < 10 g/dl) without a medical history for haemoglobinopathy and in the absence of other causes were tested for SCD. As confirmed SCD patients we accepted only anaemic patients with a suggestive medical history, plus a positive SCD test (Fig. 1). The only available laboratory investigation at the *Salam* Centre is a qualitative

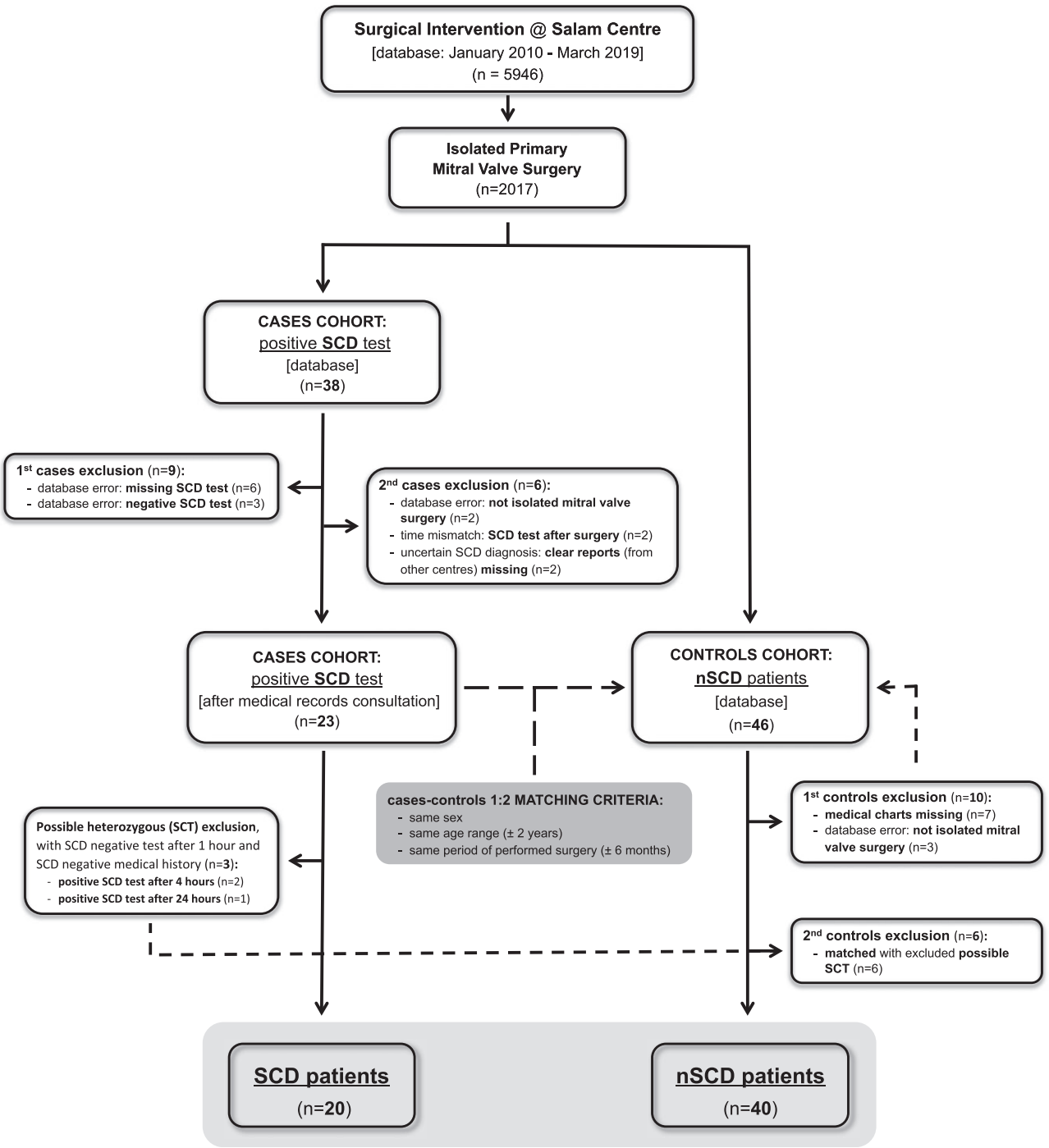

Figure 1: Study cases' cohort (sickle-cell disease) selection and relative controls cohort (non-sickle-cell disease) matching. nSCD: non-sickle-cell disease; SCD: sickle-cell disease; SCT: sickle-cell trait.

assay, the sickling test [10]. Some patients were already admitted with a positive SCD test from other facilities.

Perioperative transfusion management

During the perioperative period, all anaemic patients received packed red blood cells (pRBCs) to reach Hb levels of around 8 g/dl, taking into account also the clinical context (Table 1).

Anaesthesia and surgery

There were no differences between SCD and nSCD patients in the induction and maintenance of anaesthesia. At the end of the operation, all patients were transferred to the intensive care unit (ICU). The surgical procedures were unchanged between the groups and performed by a restricted number of surgeons.

Table 1: Sickle-cell disease patient management protocol from the *Salam* Centre for Cardiac Surgery, including sickle-cell disease diagnosis, perioperative transfusion management and cardiopulmonary bypass management (with relevant differences in comparison to non-sickle-cell disease population)

SCD patient management protocol		
SCD diagnosis		
Consider sickling test	**Severe anaemia (Hb < 10 g/dl)** and	
	Negative history for haemoglobinopathy	
	Absence of other causes	
Perioperative transfusions management		
Consider **pRBC transfusions**	Keep **Hb** levels of ∽**8 g/dl**	
	On demand: contemplate the clinical context	
Intraoperative CPB management		
Aims and purposes	SCD patients	Main note in comparison to **nSCD patients**
Reduce haemodilution	Use **smallest circuits/oxygenator**	
	Limit CPB priming volume	
	Consider **conventional ultrafiltration** kit	
Limit anaemia: keep Hb levels of ∽7 g/dl	Consider **pRBCs'** addition to *CBP priming*	
	Consider **pRBCs'** transfusion *during CPB*	
Adequate temperature control strategy	If needed (in agreement with medical team): keep perfusion fluid temperature **> 35°C**	Mild hypothermia: keep perfusion fluid temperature at 32–35°C
	Rewarm priming at 35°C	
	Use **warm** blood hyperkalemic **cardioplegia** solution at **30°C**	Cold blood hyperkalemic cardioplegia solution at 4–5°C
	Keep the patient warm before and after CPB	
Limit CPB stress	Limit CPB and ACC times	
Enhance tissue perfusion	**CPB blood flow**: **2.6–2.8 l/min/m^2**	CPB blood flow: 2.4–2.6 l/min/m^2
	65 mmHg < MAP < 80 mmHg	50 mmHg < MAP < 80 mmHg
	Monitoring: • **ABG** • **lactate** • **S_vO_2**	
Avoid hypoxemia	**Priming fluid oxygenation** before CPB initiation: **pO_2 > 50 mmHg**	
	S_vO_2 > 80%	
Avoid acidosis	7.35 mmHg < pH < 7.45 mmHg	
	Consider **sodium bicarbonate** addition	

ABG: arterial blood gas; ACC: aortic cross-clamp; CPB: cardiopulmonary bypass; Hb: haemoglobin; MAP: mean arterial pressure; nSCD: non-sickle-cell disease; pO_2: oxygen partial pressure; pRBCs: packed red blood cells; SCD: sickle-cell disease; S_vO_2: CPB circuit venous line oxygen saturation.
The bold emphasis represents the highlight the key words and the target values of our treatment protocol.

Cardiopulmonary bypass (CPB) management centre protocol includes specific interventions for SCD patients (Table 1). To limit anaemia and haemodilution, adding pRBCs to CPB priming volume was considered, with further transfusions during CPB, ensuring oxygen saturation at the circuit venous line greather than 80%. The temperature control strategy for SCD contemplates limiting perfusion fluid temperature to 35°C, with cardioplegia infusion at 30°C. Higher CPB blood flow was maintained to enhance tissue perfusion. Intermittent (20–30 min) monitoring was based on arterial blood gas (ABG), venous oxygen saturation and metabolic parameters (lactate) [11].

Data collection

Anthropometric data, medical history, cardiologic diagnoses, prognostic scores and surgical procedures (Table 2), as well as Hb levels at the predefined intervals and pRBC transfusions throughout the perioperative period (Table 3), were recorded. The lengths (days) of each hospitalization phase were also calculated.

CPB data were derived from perfusion records (Supplementary Material, Table S1). The volume of pRBCs and the overall fluids (ml) used for CPB circuit priming and throughout the whole extracorporeal assistance were recorded. The volume of pRBCs (ml)

Table 2: Data relative to study population baseline characteristics and their comparison between cases cohort (sickle-cell disease) and controls cohort (non-sickle-cell disease)

	Study population (*n* = 60)	SCD (*n* = 20)	nSCD (*n* = 40)	*P*-Value*
Age (years), median (25p–75p)	14 (9–22)	13.0 (8–22)	14.0 (9–22)	0.121
Female gender, *n* (%)	42 (70.0)	14 (70.0)	28 (70.0)	1.000
BMI (kg/m^2), median (25p–75p)	13.6 (12.2–16.6)	13.3 (11.6–15.3)	14.3 (12.7–17.4)	**0.009**
BSA (m^2), median (25p–75p)	1.10 (0.91–1.36)	1.03 (0.85–1.18)	1.19 (0.94–1.40)	**0.001**
History of blood transfusions, *n* (%)	11 (18.3)	9 (45.0)	2 (5.0)	**0.001**
preOT Hb (g/dl), median (25p–75p)	10.8 (9.4–12.6)	8.1 (7.1–9.4)	11.8 (10.0–13.0)	**<0.001**
preOT SMR, *n* (%)	43 (71.7)	18 (90.0)	25 (62.5)	0.090
preOT SMS, *n* (%)	13 (21.7)	2 (10.0)	11 (27.5)	
preOT SmixMV, *n* (%)	4 (6.7)	0 (0.0)	4 (10.0)	
ASA (*n*), median (25p–75p)	3 (3–3)	3 (3–3)	3 (3–3)	0.999
NYHA (*n*), median (25p–75p)	2 (2–3)	2 (2–3)	2 (2–3)	0.436
EuroSCORE II (%), median (25p–75p)	1.01 (0.83–1.35)	0.98 (0.73–1.14)	1.12 (0.84–1.54)	0.070
MVReplace, *n* (%)	47 (78.3)	15 (75.0)	32 (80.0)	0.630
MVRepair, *n* (%)	13 (21.7)	5 (25.0)	8 (20.0)	

*Univariate conditional logistic regression model.

ASA: American Society of Anesthesiologists; BMI: body mass index; BSA: body surface area; EuroSCORE: European System for Cardiac Operative Risk Evaluation II; Hb: haemoglobin; MVRepair: mitral valve repair; MVReplace: mitral valve replacement; nSCD: non-sickle-cell disease; NYHA: New York Heart Association score; preOT: preoperative; SCD: sickle-cell disease; SmixMV: severe mixed mitral valve; SMR: severe mitral valve regurgitation; SMS: severe mitral valve stenosis.

The bold emphasis represents the statistical significance: we have marked all the p-value < 0.05.

Table 3: Comparison between cases' cohort (sickle-cell disease) and controls cohort (non-sickle-cell disease) relative to perioperative packed red blood cells transfusions and haemoglobin values

	SCD (*n* = 20)	nSCD (*n* = 40)	*P*-Value*
Patients requiring preOT pRBCs' transfusion ($n_{patients}$; %)	9 (45.0)	0 (0.0)	**0.003**
Patients requiring postOT pRBCs' transfusion during ICU stay ($n_{patients}$; %)	8 (40.0)	16 (40.0)	1.000
Hb preOT (g/dl), median (25p–75p)	8.1 (7.1–9.4)	11.8 (10.0–13.0)	**<0.001**
Hb POD1 (g/dl), median (25p–75p)	10.1 (9.0–11.2)	10.8 (10.2–12.1)	0.616
Hb POD2 (g/dl), median (25p–75p)	9.2 (8.2–10.5)	10.4 (9.5–11.3)	0.483
Hb D/C (g/dl), median (25p–75p)	7.9 (7.2–9.5)	9.3 (9.1–10.5)	0.057

*Multivariable conditional logistic regression adjusted by BSA.

BSA: body surface area; D/C: discharge; Hb: haemoglobin; ICU: intensive care unit; nSCD: non-sickle-cell disease; POD: perioperative day; postOT: postoperative; pRBCs: packed red blood cells; preOT: preoperative; SCD: sickle-cell disease.

The bold emphasis represents the statistical significance: we have marked all the p-value < 0.05.

transfused during the CPB weaning was also recorded. ABG parameters were collected as mean values during CPB and as single score at the end of CPB (Supplementary Material, Table S1).

Perioperative morbidity was evaluated by means of the Sequential Organ Failure Assessment score [12] variables (according to the worst values during ICU stay) and also by the need for continuous renal replacement therapy, mechanical ventilation length, surgical results and complications, ICU readmission and reintubation (Table 4). Specific SCD-related complications were reported separately. Outcome was reported as hospital, 30-day and 1-year mortality (Table 4).

Statistical analysis

Categorical data are expressed as counts (percentages) and continuous variables are described as medians with interquartile range (IQR) (25th–75th percentile). Univariate and multivariable conditional logistic regression models were run to take into consideration matching, while controlling for confounders. We considered potential confounders' main patients' characteristics reported in Table 1 and found to be statistically significant ($P < 0.05$) in the univariate analysis [i.e. body mass index, body surface area (BSA), preoperative Hb levels, history of blood transfusions]. However, if the Pearson or Spearman correlation coefficient (according to variables distribution) was greather than 0.30, the variable with the lower *P*-value was retained in the model. When appropriate, the exact conditional logistic regression was fitted to address issues of separability. *P*-values lower than 0.05 were considered significant in two-tailed tests. All analyses were performed using SAS (Statistical Analysis System) software, version 9.4.

Ethics

As a retrospective study, the protocol has been reviewed and approved, waiving the consent to the use of personal data, by the Research Ethical Committee of the University of Milan (Comitato Etico, Università degli Studi di Milano, internal file number 49/20, date 14 May 2020).

Table 4: Comparison between cases' cohort (sickle-cell disease) and controls cohort (non-sickle-cell disease) relative to perioperative morbidity and mortality

	SCD ($n = 20$)	nSCD ($n = 40$)
SOFA score (*n*), median (25p–75p)	5 (3–5)	4 (3–6)
Liver failure		
Absent, *n* (%)	9 (45.0)	29 (72.5)
Mild, *n* (%)	10 (50.0)	9 (22.5)
Moderate, *n* (%)	2 (5.0)	0 (0.0)
Severe, *n* (%)	0 (0.0)	1 (5.0)
Renal failure		
Absent, *n* (%)	19 (95.0)	36 (90.0)
Risk, *n* (%)	1 (5.0)	2 (5.0)
Injury, *n* (%)	0 (0.0)	0 (0.0)
Failure, *n* (%)	0 (0.0)	2 (5.0)
CRRT, *n* (%)	0 (0.0)	1 (2.5)
Acute lung injury: absent, *n* (%)	20 (100.0)	40 (100.0)
MV length (h), median (25p–75p)	19 (11–24)	20 (14–37)
Bleeding >300 ml/24 h, *n* (%)	5 (25.0)	8 (20.0)
Chest re-exploration, *n* (%)	0 (0.0)	1 (2.5)
Pericardial tamponade and pericardiocentesis, *n* (%)	1 (5.0)	1 (2.5)
Re-intubation, *n* (%)	0 (0.0)	1 (2.5)
Cerebrovascular accident, *n* (%)	1 (5.0)	0 (0.0)
Cardiocirculatory emergency, *n* (%)	0 (0.0)	0 (0.0)
Haemolytic crisis, *n* (%)	1 (5.0)	0 (0.0)
ICU readmission, *n* (%)	1 (5.0)	1 (2.5)
MVReplace—D/C: normal MP, *n* (%)	14 (93.3)	31 (96.9)
Mild MP paraleak, *n* (%)	1 (6.7)	0 (0.0)
Moderate MP paraleak, *n* (%)	0 (0.0)	1 (3.1)
MVRepair—D/C: normal, *n* (%)	3 (60.0)	3 (37.5)
Mild impairment, *n* (%)	0 (0.0)	4 (50.0)
Moderate impairment, *n* (%)	2 (40.0)	1 (12.5)
Total hospital stay (days), median (25p–75p)	16 (12–27)	16 (9–24)
preOT hospital stay (days), median (25p–75p)	8 (5–16)	5 (2–10)
postOT hospital stay (days), median (25p–75p)	8 (7–15)	8 (6–12)
postOT ICU stay (days), median (25p–75p)	2 (1–3)	2 (2–4)
intraOT mortality, *n* (%)	0 (0.0)	0 (0.0)
ICU mortality, *n* (%)	0 (0.0)	0 (0.0)
Hospital mortality, *n* (%)	0 (0.0)	0 (0.0)
30-day mortality, *n* (%)	0 (0.0)	0 (0.0)
1-year mortality, *n* (%)	1 (5.0)	1 (2.5)

CRRT: continuous renal replacement therapy; D/C: discharge; ICU: intensive care unit; intraOT: intraoperative; MP: mitral prosthesis; MV: mechanical ventilation; MVRepair: mitral valve repair; MVReplace: mitral valve replacement; nSCD: non-sickle-cell disease; postOT: postoperative; preOT: preoperative; SCD: sickle-cell disease; SOFA: Sequential Organ Failure Assessment.

Data availability statement

The principal investigator had full access to all the data in the study and takes responsibility for its integrity and the data analysis. The data underlying this article will be shared on reasonable request by the corresponding author and the NGO EMERGENCY, which remains the sole owner of all data and results disclosed.

RESULTS

Patient enrolment

According to the *Salam* Centre's database, 5946 operations were performed in the 2010–2019 period, with 2071 isolated mitral valve surgeries; of these, 38 were flagged in the database as SCD patients. After consultation of medical records, the number of confirmed SCD patients was reduced to 20 (0.99% of isolated mitral valve surgeries) and matched to 40 nSCD patients (Fig. 1).

Study population

Overall, SCD and nSCD cohorts were comparable at the baseline, except for body mass index (13.3 [11.6–15.3] vs 14.3 [12.7–17.4] kg/m^2, $P = 0.009$) and BSA (1.03 [0.85–1.18] vs 1.19 [0.94–1.40] m^2, $P = 0.001$), and in regard to an expected positive past history of blood transfusions in the SCD patients (9 [45.0%] vs 2 [5.0%], $P = 0.001$) and a lower preoperative Hb (8.1 [7.1–9.4] vs 11.8 [10.0–13.0] g/dl, $P < 0.001$) (Table 2).

Cardiopulmonary bypass support variables

Median CPB perfusion fluid temperatures were higher in SCD patients during cooling phase (34.7 [33.0–35.9] vs 33.0 [31.5–34.2] °C, $P = 0.010$). The pharyngeal temperature was consequently higher during the cooling (34.1 [31.2–35.3] vs 32.3 [31.0–34.2] °C, $P = 0.026$) and rewarming phase (36.5 [36.0–36.7] vs 36.2 [35.8–36.5] °C, $P = 0.026$). By indexing mean CPB blood flow to BSA, a substantial greater median value was observed among SCD patients (2.83 [2.35–3.06] vs 2.54 [2.36–2.65] l/min/m^2, $P = 0.033$). To note, total CPB time (59 [47–71] vs 73 [55–93] min, $P = 0.239$) and aortic cross-clamp (ACC) time (39 [33–50] vs 47 [31–68] min, $P = 0.098$), although not statistically significant, were shorter in SCD patients (Supplementary Material, Table S1).

Intraoperative: haemoglobin, arterial blood gas and transfusions

Hb values during CPB were lower in the cohort of SCD patients (7.3 [6.5–8.8] vs 8.4 [7.9–8.9] g/dl, $P = 0.011$), with normal ABG parameters in both groups. For SCD patients, a significantly greater volume of pRBCs (300 [300–300] vs 200 [0–300] ml, $P = 0.003$) was used for the CPB circuit priming, although not significant after adjustment by BSA ($P = 0.113$). Likewise, the median volume of pRBCs used during the entire CBP support (CPB priming included) was higher in SCD patients (600 [300–600] vs 300 [250–375] ml, $P = 0.008$ and $P = 0.470$, for unadjusted and adjusted models, respectively) (Supplementary Material, Table S1).

Perioperative: haemoglobin and transfusions

Hb values were lower in SCD patients both preoperatively (8.1 [7.1–9.4] vs 11.8 [10.0–13.0] g/dl, $P < 0.001$) and at discharge, with a borderline significance (7.9 [7,2–9.5] vs 9.3 [9.1–10.5] g/dl, $P = 0.057$). The preoperative administration of pRBCs involved SCD patients only (9 [45.0%] vs 0 [0.0%], $P = 0.003$) (Table 3).

Morbidity and mortality

The perioperative complications distribution was similar for both cohorts, excepted for the frequency of increased 'mild' liver failure, in the SCD cohort (50.0% vs 22.5%, $P = 0.03$) as a consequence of the higher bilirubin levels during ICU stay (Table 4).

Specific SCD-related complications were diagnosed in two cases: a cerebrovascular accident with seizures and a haemolytic crisis. The complication was transient and did not impact the postoperative clinical course in both cases.

There were no differences in perioperative hospital length of stay, while the preoperative hospital stay was longer in SCD patients (8 [5–16] vs 5 [2–10] days), although not statistically significant after adjustment by BSA.

There were no deaths in the early in-hospital or 30-day period, while a single patient in each group died within the first year, respectively, from severe malaria and heart failure.

DISCUSSION

SCD patients undergo several surgical procedures with a well-known greater incidence of complications [3, 4], which probably leads to the under-treatment of their diseases. Anxiety, stress, dehydration, low blood flow in capillaries exposing erythrocytes to local hypoxia, hypothermia, acidosis and systemic hypoxia are commonly reported trigger events of sickling crises [1, 2]. These conditions are quite frequent during surgery and the perioperative period, especially during open-heart procedures [5].

Practising cardiac surgery in SSA [9], we have had to face the problem of SCD patients who require open-heart procedures; we agreed on a literature-based, simple protocol to limit the risk of perioperative sickling. The bundle of interventions was directed to control the supposed risk factors in a feasible way, considering the difficult context.

This study documents substantial safety for SCD patients relative to comparable nSCD patients. Any severe non-SCD-specific perioperative complication arose, although two cases presented some days later SCD-specific events: a cerebrovascular accident with seizures and a haemolytic crisis. Records from our database, regarding a greater group of unselected SCD patients with a variety of open-heart procedures (Supplementary Material, Tables S2 and S3), confirm these outcome results, although without any inclusion/exclusion criteria and matched controls.

The study does not allow us to claim the efficacy of our preventive protocol, but it shows the feasibility of safe open-heart surgery, at least mitral valve surgery, for SCD patients. Nonetheless, something intrinsic to the bundle approach is the difficulty of grading the relevance of the single interventions.

The role of transfusions is obvious: SCD patients are mostly anaemic, and they need a significantly greater amount of pRBC, as stated in other publications [13]. Nevertheless, the measured Hb levels in SCD patients were similar to those in nSCD patients soon after surgery and decreased during the perioperative period, reaching borderline significant lower values at discharge. This could be explained by the shorter lifespan of transfused pRBCs or the persisting low-grade haemolysis. The medical literature does not report enough specific evidence to establish a well-documented and widely accepted transfusion protocol taking into account the whole perioperative period, especially for cardiac surgery patients. pRBC transfusions to increase normal Hb levels and dilute HbS seem to be an obvious approach, widely applied [7, 14]. Anyhow, pRBC administration produces an increase in blood viscosity with the risk for perioperative sickling, microvascular occlusion and haemolysis that should be weighed [15]. The greater benefit of the extreme form of HbS wash-out and substitution by exchange transfusion has not been confirmed in controlled or observational studies [16–19]. Our perioperative transfusion strategy in the SCD group was more 'on-demand' than protocol based. With this approach, Hb levels of 7–8 g/dl seem adequate and higher target values [15, 20] are probably not necessary, but unfortunately we were unable to measure HbS concentration [14, 15]. Therefore, the very empirical management of transfusions in our approach seems safe where the current literature exhibits a lack of consensus [8, 15–17, 21, 22].

An essential but controversial topic in extracorporeal assistance of SCD patients is the use of systemic hypothermia [22], probably the most widely recognized risk factor for sickling [7, 20, 22–24]. According to our results, a slightly but significantly higher temperature of the perfusion fluid resulted in greater body temperature among SCD patients during CPB. Although all patients were kept within the range of mild hypothermia, the median pharyngeal temperature was higher in SCD patients compared to nSCD patients. A significant difference was observed during both the cooling (34.1 vs 32.3°C) and the rewarming phase (36.5 vs 36.2°C). This strategy proved to be safe, representing a compromise between neuroprotection [25] and exposure of SCD patients to hypothermia-related complications. Even if the risk of sickling derived from low CPB temperatures has been questioned [8], a general uncertainty persists and, considering the risk–benefit ratio, we chose a lower degree of hypothermia for our SCD patients. A strategy based on higher CPB blood flow in SCD patients (2.83 vs 2.54 l/min/m^2) was chosen to maintain adequate tissue perfusion [21, 24]. Moreover, frequent checks and accurate monitoring evidenced normal ABG parameters in both groups. This is part of the protective strategies suggested for SCD patients, aimed at maintaining homeostasis by limiting acidosis and hypoxia [7, 8, 17, 19]. Similarly, the tendency for reduced CPB time (59 vs 73 min) and aortic cross-clamp time (39 vs 47 min) reflects the effort of shortening the exposure to low flow and low body temperature states.

Interestingly, a trend for longer preoperative hospital stays of SCD patients (8 vs 5 days) could be indicative of greater requirements for perioperative optimization. The only significantly different outcome measures between the two cohorts is in the frequency of mild liver failure (50.0% vs 22.5%), depending to the increased bilirubin levels. A greater haemolytic activity is the most probable physiopathological mechanism of this transient increase [26], which did not delay significantly discharge from the hospital. There are no differences in the other outcome measures and these results seem encouraging when compared to those from other studies [6–8, 16]. However, specific hazards exist: a cerebrovascular event with concomitant seizures and a haemolytic crisis were peculiar events that underline the intrinsic perioperative risk of SCD.

Limitations

Although SCD is quite frequent in SSA countries [1], the combination with open-heart surgery remains a rare circumstance, and prospective, well-designed studies are difficult to imagine. The limits of our study are due to possible controls' selection bias, the retrospective design and the limited available resources, mainly laboratory capacity [10], since more sophisticated diagnostic tests and haematological investigations were not possible. The case ascertainment represents the main weakness of the study. However, all available measures were taken to reduce the risk of

false positives, at the cost of lessening the sample size. Furthermore, patients in the control cohort did not undergo a diagnostic test, taking into account medical history, laboratory test and clinical conditions not suggestive of SCD. We considered only isolated mitral valve surgery to elude the confounding factors that could result from different cardiac surgeries. Finally, we are aware that an analysis that had included, as controls, all eligible patients would have allowed a more accurate containment of other potential confounders (beyond gender, age and period of surgery, considered in our analysis through matching). However, the effort to retrospectively retrieve reliable data for about 2.000 patients was beyond our possibilities.

The bundle of interventions was applied as a clinical protocol and no specific data were collected. The fairly young age of our SCD patients (13 [8–22] years), who had limited multi-organ involvement from long-lasting SCD [1, 2], may also have played a part in protecting them from more severe manifestations. This limits the transferability of our results to older patients and different contexts. Notably, this study was performed in a low-income country in SSA, attempting to face a real-life problem.

CONCLUSION

According to this study and our clinical experience with SCD patients, we can conclude that SCD patients can undergo open-heart surgery with an acceptable risk profile. A preventive bundle including 'on-demand' pRBCs' transfusions, cooling limitation during CPB, alongside with higher blood flow, and strict monitoring to avoid sickling from acidosis or hypoxia led to outcomes comparable to those for nSCD patients.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

ACKNOWLEDGEMENT

The authors would like to thank the Sudanese and foreign medical and non-medical workers at the *Salam* Centre. They also acknowledge Nicoletta Erba and Flavio Puglisi for technical support, Lorenzo Valgoi for database managing and Paola Pugni, Virginia Beltrama, Giacomo Piccinno and Dimiana Saber for data sampling and reporting. Finally, the authors are grateful to George Cowie and Sofia Gatti for language revision and editing.
This work is dedicated to the memory of Gino Strada, founder of the NGO EMERGENCY and chief surgeon at the *Salam* Centre for Cardiac Surgery for many years, who spent his life fighting for the right to universal healthcare.

Conflict of interest: none declared.

AUTHOR CONTRIBUTIONS

Francesco Epis: Conceptualization; Data curation; Investigation; Methodology; Project administration; Validation; Writing—original draft; Writing—review & editing. **Liliane Chatenoud:** Formal analysis; Investigation; Methodology; Validation; Writing—review & editing. **Alberto Somaschini:** Formal analysis; Validation; Writing—review & editing. **Ilaria Bitetti:** Validation; Writing—original draft; Writing—review & editing. **Fulvio Cantarero:** Data curation; Validation. **Alessandro Cristian Salvati:** Data curation; Investigation; Validation; Writing—review & editing. **Daniela Rocchi:** Data curation; Investigation; Validation; Writing—review & editing. **Salvatore Lentini:** Data curation; Investigation; Validation; Writing—review & editing. **Elena Giovanella:** Data curation; Investigation; Validation; Writing—review & editing. **Gina Portella:** Conceptualization; Data curation; Software; Validation; Writing—review& editing. **Martin Langer:** Conceptualization; Data curation; Investigation; Methodology; Supervision; Validation; Writing—original draft; Writing—review & editing.

REVIEWER INFORMATION

Interactive CardioVascular and Thoracic Surgery thanks Carlos A. Mestres and the other anonymous reviewer(s) for their contribution to the peer review process of this article.

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