JKAU: Med. Sci., **Vol. 18** No. 4, pp: 3-15 (2011 A.D. / 1432 A.H.)
DOI: 10.4197/Med. 18-4.1

Open Heart Surgery in Patients with Rheumatic Mitral Valve Disease and Sickle Cell Disease, King Abdulaziz University Hospital: A 3 Years Experience

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Abstract. Patients with sickle cell trait or a disease who require cardiac surgery are at risk of a potentially fatal sickling crisis, which may be induced by hypothermia, hypoxia, acidosis, or low-flow states. Literature on the evaluation and specific management of these patients remains limited, and further studies are strongly recommended. This presents 3 years experience in King Abdulaziz University Hospital (2007-2009). A series of five patients with homozygous sickle cell disease and rheumatic heart disease underwent successful open heart surgery for cardiac valvular lesions, and evaluated in a retrospective nonrandom manner. Exchange transfusion was implemented in all cases, in addition to application measures to avoid/ or minimize vasoocclusive crisis. Two patients developed mild postoperative elevation of liver enzymes. One patient had perioperative low cardiac output and required inotrops and intra aortic balloon counter pulsation for one day, he required two weeks to recover from jaundice and elevated liver enzymes. All patients received anticoagulation for at least three months with no postoperative complications in their follow-up of 1-4 years. Heart valve surgery can be performed safely in patients with sickle cell disease with acceptable outcome, provided that the body environment during and after surgery is kept suitable and does not trigger vasospasm.

Keywords: Sickle cell disease, Surgery for rheumatic mitral regurgitation.

Introduction

Sickle cell disease is one of the most common genetic disorders world-wide, affecting approximately 5% of the world population. It is

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Accepted for publication: 29 May 2011. Received: 05 March 2011.

frequently seen among Afro-Caribbeans, but is also found in India, the Middle East, Southern Europe[1] and in Saudi Arabia Eastern and Western provinces. Sickle cell anemia is an inherited disease, in which the red blood cells normally disc-shaped, become crescent-shaped, causing small blood clots that give rise to recurrent episodes of sickle cell pain or vasoocclusive crisis. Complications of sickle cell disease include recurrent aplastic and hemolytic anemia, gallstones, multisystem disease (kidney, liver, lung), narcotic abuse, splenic sequestration syndrome, acute chest syndrome, and erectile dysfunction (as a result of priapism). In addition to blindness/visual impairment, neurologic symptoms and stroke, joint destruction and infections, including pneumonia, cholecystitis, osteomyelitis, and urinary tract infection[2]. As surgery in general and cardiac surgery, in specific homozygous patients, are associated with high morbidity and mortality resulting from concurrent hypothermia and low-flow state during operation[3], therefore, special care and specific precautions are required perioperatively to minimize the surgical risk.

Patients and Methods

A series of five patients with homozygous sickle cell disease who underwent mitral valve surgery +/- and additional valve surgery were tracked retrospectively for three years (from January 2007 to December 2009). All patients had history of regular multiple blood transfusions. They all had severe mitral valve regurge isolated or combined with regurge of other cardiac valves, and they had congestive heart symptoms of NYHA class III or IV as described below:

- Case 1: severe MR with severe AR (post infective endocarditis).
- Case 2: severe MR with severe TR.
- Case 3: severe MR with severe TR.
- Case 4: severe MR and moderate TR.
- Case 5: sever MR with sever AR.

All patients underwent exchange transfusion before, during and after surgery along with other measures to avoid sickling, which included normothermic cardiopulmonary bypass, maintaining high perfusion pressure, correcting acidosis and avoiding hypoxemia.

All patients received anticoagulation for at least three months after surgery.

Patients' characteristics: three females and two males with a mean age 22.8 (range 11-35 years).

Hematological data of all patients are summarized in Table 1.

Data of echocardiography findings of all patients are summarized in Table 2.

Table 1. Results of blood testing.

	Preoperative	Postoperative
Hemoglobin (g/dl)	7.54 (6.5-8.2)	8.88 (8.4-9.5)
Hematocrit %	23.616 (20.1-28.8)	26.18 (22.9-29.6)
MCV	76.42 (69-86.3)	83.86 (72.2-90)
Platelets (10^3/1)	284.4 (155-595)	227.6 (76-589)
Serum ferritin (ng/ml)	574.46 (115-895)	634 (235-920)
HB S %	79.32 (60.2-89)	50.94 (22.7-88)
HB F %	5.44 (4.6-6.1)	3.64 (0.7-5.3)
HB A2%	2.64 (2.3-2.8)	18.6 (2.4-74.3)
Reticulocyte %		3.58 (1.3-7.1)

Table 2. Results of echocardiography findings.

	Pre operative	Post operative
PASP (mmHg)	72.8 (54-95)	61.8 (45-85)
Left Atrial size (mm)	6.72 (5.4-8.3)	6.2 (4.6-7.6)
Right ♀Atrial size (mm)	4.18 (3.5-4.7)	4.0 (3.4-4.5)
LVIDD (mm)	6.84 (5.6-8.2)	6.4 (5.1-7.3)
LVIDs (mm)	4.94 (3.8-5.6)	4.7 (3.6-5.2)
Ejection Fraction (%)	45.8 (35-59)	54.8 (38-59)

Pre operative Protocols

Anesthesia and surgery protocols applied to all patients were as follows:

Preoperative blood transfusion was given the day before surgery to achieve hemoglobin level at or near 10, hematocrit of 30-35%, and HbS concentration level less than 10%.

Pre-medication with diazepam 0.1 mg/kg was given orally on the night before the operation and morphine sulfate 0.2 mg/kg i.m. one hour before operation.

Monitoring by peripheral intravenous lines, radial artery catheter inserted using local Xylocaine 2%, electrocardiographic monitoring of lead II and V5, and pulse oximetry, Non invasive and invasive arterial pressure, capnography after endotracheal intubation, nasoesophageal and rectal body temperature were also monitored.

Anesthetic management and surgical techniques: standard anesthesia induction with intravenous sufentanil 1-2 μg/kg and midazolam 10-20 μg/kg i.v., rocuronium 0.5 mg/kg i.v. for muscle relaxation and endotracheal intubation.

Patients were mechanically ventilated with oxygen/air (inspired oxygen fraction 0.5), and end tidal carbon dioxide was kept at a range of 30-35 mmHg using the closed circuit of the anesthesia machine (Dragger Zeus, Germany). After induction of anesthesia and patient stabilization, a triple lumen central venous catheter was inserted through the right internal jugular vein. Anesthesia was maintained with continuous infusion of propofol 50-100 μg/km/min and sufentanil 0.25-0.5 μg/kg i.v. boluses. In addition to sevoflurane supplementation when required to maintain the arterial blood pressure and heart rate within 20% of the preoperative values. Muscle relaxation was maintained with continuous rocuronium infusion 0.6 mg/kg/hr. All operations were performed through median sternotomy incisions and the basic standard surgical techniques of cardiac surgery. Before aortic cannulation, all patients were anticoagulated with intravenous heparin 4 mg/kg. Cardiopulmonary bypass was conducted with a flat sheet membrane oxygenator using non-pulsatile flow. The circuit prime included 2-3 units backed red blood cell in addition to ringer's lactate solution 500-1000 ml, mannitol 50-100 ml and heparin 5000-6000 IU. The pump flow was maintained at 2-2.5 liters/min/m^2. The blood pressure during bypass was maintained at 70 mmHg or above, blood oxygen saturation at 98%-100%, and the patient temperatures were kept above 35°C throughout the procedure by using the warm mattress. After cross clamping, antegrade blood cardioplegia 1:4 (800-1000 ml) was initially infused in the aortic root to achieve cardiac arrest, which was maintained during cross clamp

by repeated infusion of 300-500 ml every 30 min through the aortic root, or directly into the left and right coronary arteries.

After ensuring adequate hemostasis of suture lines, patients were re-warmed to 37-37.5°C. Weaned off cardiopulmonary bypass and protamine sulfate was infused to neutralize heparin effect in 1:1 dose ratio.

Performed Procedures

1. One patient had aortic valve and mitral valve replacement (mechanical valves).
2. One patient had mitral valve replacement and tricuspid valve annuloplasty.
3. One patient had mitral valve annuloplasty
4. One patient had mitral valve triangular resection and annuloplasty
5. One had aortic valve and mitral valve replacement (mechanical valves).

Post-operative Intensive Care Protocols

All patients arrived at the ICU ventilated; they were maintained on sedation and muscle relaxants, on warming mattresses and blankets to keep body temperature at 37-37.5°C, plus ventilation was maintained on controlled mode with a tidal volume of 10-15 ml/kg and rate of 10-15 breath/ minute. Pressure support 10 cm H2O with initial FIo2 of 50% settings were titrated according to the ABGs and O2 saturation results to maintain SpO_2 saturation more than 95% and $Paco_2$ at 35-40 mmHg. Inotrops (Dopamine &/or adrenaline) infusion were used as required to maintain adequate blood pressure and initial arterial blood gas assessments. Additionally, laboratory investigations were performed 30 min after arrival to the ICU and repeated as required to assess and treat any derangements. When patient hemodynamic stability was ensured and there was no concern about any excessive bleeding, muscle relaxants and sedation was decreased to assess neurological function. After the patients became conscious; responding and obeying command with $S_pO_2 > 95\%$ on $FiO_2 < 40\%$, pressure support < 5 cm H2O, vital capacity > 12 ml/kg, maximum inspiratory pressure > -25 cm H2O and core body temperature > 37, plus stable hemodynamics SBP 90-110 mmHg on

minimal inotrops, they were shifted to SIMV mode and were weaned off the ventilator.

Postoperative hypertension SBP > 140 mmHg was treated with intravenous infusion of nitroglycerine 0.5-5.0 μg/kg/min as needed.

All patients were started on IV/Subcutaneous anticoagulation after ensuring no excessive bleeding, and they were started on oral anticoagulation in ICU. Heparin was stopped after INR levels reached more than 2; oral anticoagulation was stopped after three months in the case of valve repair and tissue valve replacements, and continued for mechanical valve replacements.

All patients received anticoagulation for at least three months; patients with mechanical valves were maintained on oral anticoagulation. INR 2.5-3.0 was given for those who had mitral valve replacement and INR 3.0-3.5 for patients with aortic and mitral mechanical valves.

Outcome

Out of all operated patients, two (Patients 2 & 5) developed mild postoperative jaundice and mild elevation of liver enzymes for few days. One of them (Patient 1) had perioperative low cardiac output and required inotrops and intra aortic balloon counter pulsation for one day. Additionally, he required one week to recover from jaundice and elevated liver enzymes. No other perioperative or postoperative complications were encountered in this series throughout the follow up period, which ranged between 36-48 months.

Laboratory data for all patients are listed in Table 3:

Table 3. Detailed laboratory data.

Pt		HB	HCT	Plets	PRBC	DBIL	TBIL	ALT	AST	GGT	ALP
1	Preop.	6.8	16.6	206	2	68	90	49	90	69	184
	Day 0	9.1	29.1	111	6	76	143	54	82	49	147
	Day 1	10.1	26.4	149		120	168	48	79	44	152
	Day 3	10.2	29.7	149		89	124	46	72	46	167
	Day 5	99	28.3	163		61	86	44	66	58	149
2	Preop.	6.4	16.4	151	1	37	84	38	69	38	84
	Day 0	9.5	22.9	198	4	47	78	39	89	33	96
	Day 2	8.9	27.5	185		68	110	41	92	40	102
	Day 5	8.8	24.4	204	1	67	76	40	79	39	92

Table 3. ***(Continuation)*** **Detailed laboratory data.**

Pt		HB	HCT	Plets	PRBC	DBIL	TBIL	ALT	AST	GGT	ALP
3	Preop.	7.1	21	226	1	19	63	34	43	41	37
	Day 0	9.6	28	89	4	152	252	54	87	55	49
	Day 1	8.9	26.9	103	1	81	103	42	51	71	45
	Day 3	8.4	25	152	1	79	64	35	42	67	39
4	Preop.	7.1	22.7	711	2	7	33	26	25	39	129
	Day 0	9.4	25.8	695	4	12	39	30	77	114	95
	Day 1	11.1	30.7	589		38	73	27	85	67	128
	Day 3	10.8	28.1	635		20	48	30	65	69	92
	Day 5	8.9	27.2	633		10	34	29	46	105	95
5	Preop.	6.5	18.2	299	2	13	54	41	55	99	90
	Day 0	9.1	27.5	281	6	68	134	40	64	55	66
	Day 1	9.9	28.2	265	2	98	114	37	76	42	81
	Day 3	9	25.3	257		63	93	36	54	47	96
	Day 5	8.5	24.3	307		58	72	34	44	51	86

Discussion

Sickle cell hemoglobinopathy is a recessively inherited genetic disorder that results from the mutation of the substitution of adenine for thymidine, which further ends up matching with valine rather than glutamine at the sixth codon of chromosome 11, *i.e.*, the β-globin gene[3,4]. The disorder may present as SCD, the severe form in which the fractional concentration of HbS ranges between 70% and 98%. Also, it can be manifested as SCT, which is rather benign in which the fractional concentration of HbS is < 50%[[4,5]. The solubility characteristics of HbS are severely affected, and after dispersal of oxygen to tissues, the molecule adopts its characteristic sickle shape. Erythrocytes containing high amounts of HbS undergo multiple sickling and desickling events, deforming their conformation and eventually resulting in autolysis and anemia. Furthermore, these deformed cells have an increased tendency to adhere to the vascular endothelium, frequently leading to occlusion of small-caliber vessels and causing organ damage[4]. The classic precipitating factors for sickling include stress, exposure to cold, dehydration, infections, hypoxia, inflammatory cascades, and acidosis[1,6]. Such conditions lead to potassium efflux, causing formation of insoluble globin polymers. These molecules increase the viscosity of

blood and lead to vasoocclusive phenomena, which include cell sickling, adherence of sickle cells to the endothelium, and vasoocclusion[5,7].

The risk of an intraoperative crisis due to sickle cell disease is the major consideration in cardiovascular surgery. The low oxygen tension and acidosis is expected on cardiopulmonary bypass; because the artificial circulation is wholly controlled by the perfusionist, this may trigger a crisis of profound magnitude. It is generally agreed that avoidance of acidosis, maintenance of adequate blood flow and oxygen tension during cardiopulmonary bypass, and close monitoring of laboratory results are essential in the management of sickle cell patients[8-11]. Therefore, continuous online arterial oxygen tension, acid-base balance, and temperature control are essential. Intra- and postoperative control of hemodynamic parameters, regular checking of the hematocrit to keep it at 20%-30%, electrolytes, blood gases, avoidance or minimization of postoperative pain are important in these patients. Although, it is preferable to avoid hypothermia, which will cause vasoconstriction, a number of studies have employed mild to moderate cooling without adverse effects[10,12]. Reviewing the literature and our own cases, it was observed that normothermic bypass, allowing the temperature to drift, and using only cold cardioplegia at 4°C were the safest options, especially when operating on high-risk and large numbers of cases[8,9,11,13,14]. Warm blood cardioplegia, with its high potassium concentration, may have a deleterious effect on patients with impaired renal function.

Pre- or intraoperative partial exchange transfusion have been recommended and implemented in the majority of cardiac patients to reduce the percentage of HbS[8,10,13,14]. At least 30% of the circulating plasma volume is sequestered to improve the quality of the perfusate, increase oxygen delivery, and decrease the risk of a sickle cell crisis during bypass. In a few case reports, exchange transfusion was not implemented[9,12]. In our cases, exchange transfusion was performed once intraoperatively after cannulating and before going on bypass. The perfusionist drained 500-1,000 ml of blood from the venous reservoir, depending on the patient's body weight, and replaced it with 1-2 units of packed red blood cells. Hemofiltration increases hematocrit, platelet count, and clotting factors, helps potassium removal, reduces complement activation, removes extracellular water, and helps in avoiding acidosis. There are several reports of favorable but sometimes

of variable effects of hemofiltration, especially in pediatric patients[8,10,15-17].

Stress is another major factor that may lead to sickling. Cardiac surgery itself constitutes a major stress for the patient, but the preparatory phase for operation, including intubation and the insertion of catheters, contributes considerably toward this stress, particularly in pediatric patients. Therefore, it is strongly recommended that patients be kept fully sedated during this phase[5,8,18]. Prevention of hypothermia in the operating theater is an easy preventive measure that is very helpful in avoiding sickling phenomena. Warm-air blankets before and after surgery may be helpful to stabilize the patient's body temperature[5].

Valve repair remains the procedure of choice to avoid prosthetic valve-related complications, especially hemolysis, anticoagulant use, and infection[6,8-10,12]. Several reports record no preference for tissue valves over mechanical valves[9-12,19]. Others, stipulated that mechanical valves should be avoided to minimize the risk of hemolysis which may induce a crisis in sickle cell patients[8]. Given the shorter life expectancy of these patients and the risks of mechanical valve hemolysis, bioprosthesis calcification, and reoperation, we prefer to use mechanical valves for patients < 30-years-old with non-repairable valves, and biological valves for older patients. Postoperative pain management is helped by giving multiple analgesia dosages. Prophylactic antibiotic therapy is important to minimize the risk of infection.

Conclusion

Although, open heart surgery was considered hazardous for patients with sickle cell disorders due to presence of predisposing factors inherited with the operative procedure that carry the potential of triggering sickling among operated patients. Nevertheless, the observed outcome among our cases who underwent different valve procedures, with acceptable outcome emphasizes the tolerance of these patients to these types of operations, provided that the body environment during and after surgery are kept suitable and do not trigger vasospasm.

Four other patients with the heterozygous form (sickle cell trait), also underwent valve procedures by the author in another institution, without any problems; these were not as critical as the homozygous cases. The world literature is deficient, with no major scientific

contribution to help this subset of cardiac surgery patients, except for sporadic cases, mostly reported more than a decade ago.

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جراحة القلب المفتوح لمرضى الأنيميا المنجلية المصابين بتلف الصمام الميترالى الناتج عن مضاعفات الحمى الروماتيزمية للقلب، خبرة مستشفى جامعة الملك عبدالعزيز على مدى ثلاثة سنوات

حسين حمزة جباد

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جدة – الملكة العربية السعودية

المستخلص. مرضى الأنيميا المنجلية المصابين بتلف الصمام الميترالى الناتج عن مضاعفات الحمى الروماتيزمية، والذين يحتاجون إلى إجراء عمليات القلب لترميم، أو تغيير الصمام الميترالى، يتعرضون إلى مخاطر تحول كرات الدم الحمراء إلى شكل المنجل وسد الأوعية الدموية، مما يؤدى إلى أزمات قد تهدد الحياة. ومع تطور تقنيات التشخيص والعلاج، ازداد عدد هؤلاء المرضى، ولكن البحوث العلمية فى هذا المجال لا تزال محدودة. وقد قمنا بمراجعة بيانات خمسة حالات متتابعة لمرضى أنيميا منجلية متوارثة من الوالدين أجريت لهم بنجاح عمليات جراحة قلب مفتوح لترميم أو تغيير الصمام الميترالى مع أو بدون صمامات أخرى. وقد تم إجراء نقل واستبدال وحدات من الدم قبل إجراء الجراحة لكل المرضى، بهدف تقليص المضاعفات. بعد الجراحة تعرض اثنان من المرضى لارتفاع بسيط فى انزيمات الكبد لعدة أيام، واحتاج مريض آخر إلى أدوية دعم الدورة الدموية، وجهاز الضخ البالونى فى الشريان الأورطى لمدة يوم واحد، وارتفعت إنزيمات الكبد لهذا المريض لمدة أسبوعين. ولم

تحدث أى مضاعفات أخرى خلال فترة مراجعة من ١-٤ سنوات.

الاستنتاج: يمكن إجراء جراحات القلب المفتوح لمرضى الأنيميا المنجلية بنتائج مرضية، عند توفر الاحتياطات اللازمة قبل، وأثناء، وبعد إجراء الجراحة.