Perioperative management of a paediatric cardiac surgical patient with Glucose-6 Phosphate Dehydrogenase deficiency

Jeril George Kurien

Department of Paediatric Cardiac Sciences, Sir H.N. Reliance Foundation Hospital, Mumbai 400004, India

Correspondence to Jeril George Kurien, Chief Paediatric Cardiac Anaesthesiologist & Intensivist, Department of Paediatric Cardiac Sciences, Sir H.N. Reliance Foundation Hospital, Mumbai 400004, India.
Mobile No: +91 9769004541/+91 8369352661;
e-mail: jeril.kurien@rfhospital.org / drjgk@rediffmail.com

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Glucose-6-Phosphate Dehydrogenase (G6PD)-deficiency is one of the most common enzymatic disorders of Red Blood Cells (RBCs). Cardiac surgery involving conventional Cardiopulmonary bypass (CPB) in such patients pose an increased risk of haemolysis as well as impaired oxygenation leading to prolonged ventilation. Many commonly used drugs also predispose such patients for haemolysis when they are subject to surgery. Here we describe a successful perioperative management of a 3 year old child, a known case of G6PD- deficiency who presented with a diagnosis of Atrial septal defect (ASD) with Partial Anomalous Pulmonary Venous Connection (PAPVC) and Mild-Moderate Mitral Regurgitation & underwent surgery with preplanned precautionary measures avoiding haemolysis.

Keywords:
Glucose -6-Phosphate dehydrogenase deficiency, Red blood cells, Cardiac surgery, Cardiopulmonary bypass, haemolysis

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Introduction

Glucose-6-Phosphate Dehydrogenase (G6PD) – deficiency an X-linked disease is one of the commonest enzymatic disorder of RBCs in humans affecting about 400 million people all over the world. According to WHO, the prevalence in India ranges from 1–27% in different communities and regions with higher prevalence among the tribal population [1,2]. G6PD enzyme catalyses the first step in the pentose phosphate pathway, leading to the production of antioxidants. A G6PD- deficit patient lacks the ability to protect RBCs against oxidative stress, from certain medications, infections, metabolic conditions. During cardiac surgery, events like perioperative ischemia, reperfusion, circulation of whole blood through CPB circuit, hypothermia, acidosis, hypo perfusion & hyper perfusion can all lead to production of free radicals. The RBCs of G6PD-deficient patients are unable to scavenge these free radicals, resulting in haemolysis. Here we describe the anaesthesia management of a G6PD- deficient child who underwent cardiac surgery at our institute after preplanned precautionary measures.

Case history

A 3 year old, 15 kg male child was referred by a cardiologist with a diagnosis of a major heart defect. He had history of repeated chest infections and was known case of G6PD-Deficiency (<10% activity). (Table 1) Mother was also G6PD-deficient. On Examination, saturation was 98% on room air, Heart Rate 112/min, warm peripheries, and well felt pulses. Echocardiogram revealed : large secondum ASD (shunting left to right), Right sided pulmonary veins draining anomalously to Right Atrium, Mild to Moderate Mitral Regurgitation, Mild Tricuspid Regurgitation (TR), Mild valvar Pulmonary Stenosis, Peak Systolic gradient of 27 mmHg across valve, Pulmonary annulus 27 mm, estimated Right Ventricular pressure by TR jet 45 mmHg and normal biventricular function. Preoperatively routine blood investigations were evaluated including Total Counts, Reticulocyte Count & Lactate Dehydrogenase (LDH)

He was electively posted for correction of anomalous pulmonary venous connection + fenestrated ASD closure + Mitral valve repair.

Drugs known to cause haemolysis in G6PD-deficient patients were listed & avoided after consultation with a Haematologist.

Table 1 G6PD Activity test

Test	Patient	Reference range
G6PD Qualitative (min)	>120	0–60 not deficient 60-120 partial deficient > 120 G6PD-deficient
G6PD Quantitative U/g Hb	0.50	7–20.5

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Preoperatively, Allopurinol 100 mg 6 hourly was started and 200 ml Leucodepleted Packed RBCs was transfused over 3 hrs followed by 5 mg intravenous Furosemide. Child was kept nil orally for 4 hours, IVFluids Plasmalyte started @ 30 ml/h & premedicated with Triclofos on the morning of surgery. In the theatre, all routine haemodynamic monitors as per American Society of Anesthesiology (ASA) standards were attached and Anaesthesia was induced with intravenous Glycopyrolate 0.08 mg, propofol 30 mg and Fentanyl 30 ug and rocuronium 30 mg for muscle relaxation. Anaesthesia was maintained with intravenous infusions of Fentanyl 2 ug/kg/h and Dexmedetomidine 0.25 ug/kg/h & along with Sevoflurane as an Inhalation agent with intermittent boluses of 0.25 mg intravenous Vecuronium. The patient had an episode of Supraventricular Tachycardia & so Cardiopulmonary Bypass (CPB) was instituted early after Heparinisation by Aorto – Bicaval cannulation & normothermia (34° Celsius). Antegrade normothermic blood cardioplegia was used every 15 min for myocardial protection. Mitral Valve annuloplasty was done and a large pericardial patch employed to tunnel the PAPVC to the Left atrium and close the ASD and a small fenestration created in the patch. Patient was weaned from CPB with ionotropic support of Adrenaline 0.1 ug/kg/min, Milrinone 0.3 ug/kg/min and Calcium 6 ml/kg/day iv. Total Bypass time was 1hr11mins and Aortic cross clamp time was 32 min Heart rate was 102/min, Arterial Blood pressure of 90/58 mmHg, Central venous pressure 7–8 mmHg, Right Ventricular pressure 28/4 mmHg, Pulmonary Artery pressure 20/14 mmHg & Left Atrial pressure by needle 13/8 mmHg. Child was Extubated in the ICU after 2 hours of shifting. Intravenous Fentanyl 1–2 ug/kg/h and Dexmedetomidine 0.25–0.5 ug/kg/h infusions were continued into the postoperative period till removal of drains and delining. Postoperative echocardiography was normal, haemodynamics were monitored and there were no clinical or laboratory evidence of haemolysis (Table 2) Child had 2 episodes of fever and was started on Injectable Piperacillin and discharged on day 6 with stable haemodynamics.

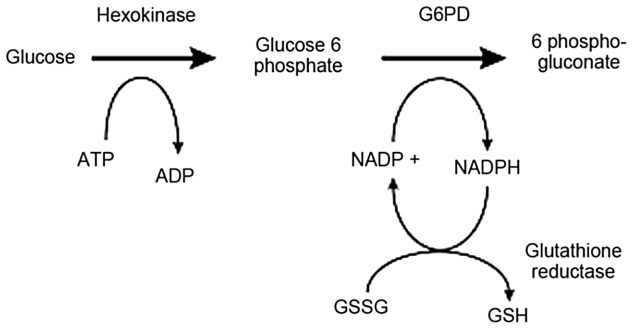
Discussion

G6PD- deficiency is an X-linked inherited disorder, most commonly present in individuals of African (A-form 10%) or of Mediterranean descent (Italians/Greeks/Arabs/Sephardic Jews) [3]. G6PD is an enzyme that catalyses the first step in the HMP/Pentose phosphate pathway (PPD). (Fig. 1.). The main end product of the HMP/PPD pathway is reduced Nicotinamide dinucleotide diphosphate which maintains the reduced glutathione within the cells and serves as antioxidant, minimizing the oxidative injury to cells (mainly RBCs) by free radicals [4].

The WHO has classified the different G6PD according to the enzyme deficiency into five variants (Table 3.) [5] and our patient belonged to Class II.

The clinical expression of this disorder includes anaemia, jaundice and reticulocytosis, all

Figure 1



Pentose phosphate pathway. G6PD catalyses NADP+ to its reduced form, NADPH, in the pentose phosphate pathway. (G6PD=Glucoseâ 6â phosphate dehydrogenase; ATP =Adenosine triphosphate; ADP=Adenosine diphosphate; NADP+ =Nicotinamide adenine dinucleotide phosphate [oxidized form]; NADPH=Reduced NADP; GSSG=Oxidized glutathione; GSH=Reduced glutathione.

Table 2 Lab investigations

Test	Normal range	Preoperative	Postop Day1	Postop Day2
Hb (g/dl)	11-14	10	11.6	11.1
TLC (109/L)	5-15	10.21	16.7	18.01
Neutrophils %	-	37.5	86.9	75.4
Lymphocytes %	-	53.9	6.4	14.5
Absolute Reticulocyte count (10^9/L)	20-120	66.7	62.7	-
Immature Reticulocyte fraction (%)	3.1-13.5	17.2	29.10	-
Reticulocyte Haemoglobin equivalent [Ret-He (pg)]	30.2-36.2	20.8	21.8	-
LDH (U/L)	120-300	271	298	-
Conjugated Bilirubin (mg/d L)	< 1	0.2	0.6	-

Table 3 WHO has classified the different G6PD variants

Class I	severe enzyme deficiency (≤10% of normal) with chronic haemolytic anaemia
Class II	severe enzyme deficiency (≤10% of normal), with intermittent haemolysis
Class III	moderate enzyme deficiency (10 to 60% of normal) with intermittent haemolysis with significant oxidative stress
Class IV	Very mild or no enzyme deficiency
Class V	Increased enzyme activity (more than twice normal)

consequences of haemolysis. Haemolysis usually occurs after exposure to drugs or to other substances that produce peroxide, resulting in oxidation of haemoglobin and red blood cell membranes [6].

Perioperative management of a paediatric patient with G6PD-deficiency for cardiac surgery is quite challenging since many events (preoperative anxiety & hypothermia to intraoperative stress and inflammation to postoperative pain) and a number of drugs (including anaesthetic medications) can lead to increased oxidative stress and production of free radicals which can trigger significant haemolysis [7,8]. (Table 4) The severity of haemolysis in G6PD-deficient patient depends on the offending agent and the enzymatic activity of the patient.

Preoperative administration of allopurinol and transfusion of leucodepleted packed RBCs was on the advice of the haematologist as a precautionary measure for attenuating any postischaemic reperfusion injury, though there is insufficient evidence in literature regarding its usage in paediatric cardiac surgery.

We have used triclofos as premedication preoperatively. Altikat *et al.* [8] studied the effects of certain anaesthetic agents on the enzymatic activity of G6PD. They found that, although isoflurane, Sevoflurane, diazepam and midazolam had an inhibitory effect on G6PD activity in vitro, halothane, ketamine & prilocaine had none. There are no reports of propofol or fentanyl or neuromuscular relaxants causing haemolysis in G6PD-deficient patients in vivo. We used propofol & fentanyl for Induction of Anaesthesia and rocuronium for muscle relaxation. The data regarding the ideal volatile anaesthetic agent for maintenance has been controversial and hence we used sevoflurane (1 Mac) as inhalation agent with fentanyl & dexmedetomidine iv infusions & intermittent boluses of vecuronium during the surgery.

Induction of CPB with circulation of blood through the bypass circuit activates the inflammatory cascade

Table 4 Safe and unsafe Drugs, Chemicals and Anaesthetic agents in the G6PD-Deficient population

Unsafe for Class I,II and III	Safe for Class II and III
Acetanilid	Acetaminophen
Dapsone	Aminopyrine
Furazolidone	Ascorbic acid
Methylene Blue	Aspirin
Nalidixic acid	Chloramphenicol
Naphthalene	Chloroquine
Niridazole	Colchicine
Nitrofurantoin	Diphenhydramine
Phenazopyridine	Isoniazid
Phenylhydrazine	L – DOPA
Primaquine	Menadione
Sulfacetamide	Paraaminobenzoic acid
Sulfamethoxazole	Phenacetin
Sulfapyridine	Phenytoin
Thiazosulfone	Probenecid
Toluidine blue	Procainamide
Trinitrotoluene	Pyrimethamine
	Quinidine
Anaesthetic Agents	Quinine
Diazepam	Sulfamethoxypyridazine
Isoflurane	Streptomycin
Sevoflurane	Sulfisoxazole
	Tripelennamine
	Trimethoprim
	Anaesthetic Agents
	Halothane
	Prilocaine
	Ketamine
	Fentanyl
	Propofol
	Benzodiazepines (except Diazepam)

As per in vitro studies done by Altikat et al [8].

with production of O2 free radicals which may provoke oxidative damage, cell injury and death in susceptible RBCs. This can affect the pulmonary oxygenation and can be especially life-threatening in cyanotic patients and patients with intra or extra cardiac shunts [9–11].

Perioperative acidosis and hyperglycaemia can also induce haemolysis during CPB and should be prevented or treated aggressively [6].

Hypothermia is a common risk factor for postoperative haemolysis which was demonstrated by Gerrah *et al.* [11] in his study of 42 patients. In our patient, we maintained nasopharyngeal and rectal temperature of 34 degrees celsius during bypass and patient showed no sign of haemolysis

We maintained high pump flows, normothermia, optimal delivery of cardioplegia, swift cardiac arrest, limited duration of CPB time (1 h 11 min), avoided acidosis and hyperglycaemia along with addition of

steroids and mannitol, thus preventing oxidative damage during CPB.

Postoperatively we continued intravenous Fentanyl 1–2 ug/kg/h & Dexmedetomidine 0.25–0.5 ug/kg/h infusions till removal of drains & delining.

Postoperative infection [12] can lead to haemolysis in such patients, so in view of febrile episodes and in spite of normal counts, we switched over from cefuroxime to piperacillin-tazobactum after sending blood cultures and stopped once cultures were negative and patient clinically asymptomatic.

Conclusion

Perioperative management of a G6PD-deficient child for cardiac surgery involves strategies to prevent haemolysis by avoiding oxidative stressors. It includes detailed preoperative evaluation, use of safe drugs for induction and maintenance of anaesthesia, maintenance of normothermic bypass, short CPB time, avoidance of oxidative drugs for Intraoperative and postoperative analgesia, maintaining good urine output and early recognition & intervention of postoperative infection.

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Conflicts of interest

There are no conflicts of interest.

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