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Management of glucose 6-phosphate dehydrogenase (G6PD) deficient patients undergoing open-heart surgery

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Abstract

Background: There are scarce studies on the management of glucose 6-phosphate dehydrogenase (G6PD) deficient patients during cardiac surgery. The purposes of this retrospective study were to present and evaluate our experience with G6PD deficient patients who underwent cardiac surgery with cardiopulmonary bypass (CPB).

Methods: We included 20 patients with G6PD deficiency who had cardiac surgeries from 2015 to 2019. We used free radical scavenging strategy and careful perioperative management. The patients were compared to a control group of 20 patients with normal G6PD enzyme activity who underwent the same type of operations in the same period.

Results: Males represented 80% of G6PD deficient patients. There were significant elevations in preoperative total bilirubin (1.03±0.33 vs. 0.57±0.11 mg/dl, p< 0.001) and reticulocytes (1.87±0.62 vs. 0.54±0.18%) in G6PD deficient patients. Valve surgery was done for 60% of G6PD deficient patients. There were no significant differences between both groups regarding the type of surgery, aortic cross-clamp, CPB, and total operative time. G6PD deficient patients had significantly lower postoperative hemoglobin levels (9.44±0.94 vs. 10.0±0.59 g/dl, p= 0.04) and significantly higher postoperative total bilirubin (1.51±0.51 vs. 0.98±0.45 mg/dl; p=0.002) and reticulocytes (1.85±0.51 vs. 0.57±0.13%; p< 0.001). There was no significant difference regarding postoperative urea and creatinine levels. Ventilation time (10.3±2.7 vs. 8.2±1.9 hours; p=0.01), ICU stay (3.1±0.87 vs. 2.3±0.71 days; p=0.004), and hospital stay (3.1±0.87 vs. 6.0±1.02 days; p<0.001) significantly increased in G6PD deficient patients. The mortality rate was 5% (one patient) in G6PD deficient patients.

Conclusion: Despite the management strategy, G6PD deficient patients undergoing cardiac surgery are more liable to hemolysis and hypoxia with more need for blood transfusion and longer ventilation time, ICU, and hospital stays when compared to patients with normal G6PD enzyme activity. Further research to improve the outcomes in G6PD deficient patients is required.

KEYWORDS
G6PD deficiency; Cardiopulmonary bypass; Free radical scavengers; Mannitol; Allopurinol hemolysis

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Introduction

Glucose 6-Phosphate Dehydrogenase (G6PD) deficiency is an X-linked genetic disorder. It is prevalent in Sub-Saharan Africa, the Middle East, and Asia [1]. The prevalence of G6PD deficiency in the Sultanate of Oman is high, 25% in males, and 10% in females [2]. G6PD deficiency leads to a decrease in reduced glutathione production, which will not be enough to protect cells from oxidative stress. Consequently, the cell membrane bursts (hemolysis), which may be a deadly matter [3-6]. G6PD deficiency potentiates the harmful effect of free radicals [7-9].

The World Health Organization (WHO) [10] classified G6PD genetic variants into five classes. Perioperative ischemia, contact of blood with circuit tubes, hypothermia, hypoperfusion, acidosis, and reperfusion, that involved in cardiac surgery with cardiopulmonary bypass (CPB) potentiate the harmful effect of free radicals in G6PD deficient patients [3,11,12].

The studies on G6PD deficient patients undergoing CPB are rare. The study aims to present and evaluate the efficacy of perioperative strategies that we used to minimize hemolysis for G6PD deficient patients undergoing open-heart surgeries on cardiopulmonary by using mannitol and allopurinol as free radical scavengers and avoidance drugs that suspected to trigger hemolysis of red corpuscles.

Patients and Methods:

This retrospective observational study was conducted on 20 patients who had moderate to severe form of G6PD deficiency (WHO class I, II, and III). We compared patients with G6PD deficiency to 20 patients with normal G6PD enzyme activity (control group). All patients underwent cardiac surgery using cardiopulmonary bypass (CPB) between January 2015 and April 2019. We did not exclude any patient with G6PD deficiency. None of our patients had recent hemolytic crises. The selection of the patients in the control group (20 patients) was performed from 956 patients with normal G6PD enzyme activity who operated at the same period using our computerized database considering age, sex, type of operation, and comorbidities.

All data were retrospectively collected, including history, and laboratory investigations (preoperative and daily postoperative hemoglobin, hematocrit, bilirubin, reticulocyte count, creatinine, and blood urea). The protocol used for G6PD deficiency patients A multidisciplinary team from cardiac surgeons and hematologists managed and followed the patients from admission until hospital discharge.

Preoperative:

Good urinary flow was maintained using intravenous mannitol 0.5 g/kg once daily and Furosemide 10mg thrice daily to prevent any renal tubular injury due to free hemoglobin. Allopurinol 600mg was given orally in the preoperative night and repeated 2 hours before surgery.

Operative:

Patients were premedicated with glycopyrrolate. Anesthesia was induced with propofol and fentanyl. Atracurium was given to facilitate tracheal intubation, and anesthesia was maintained with isoflurane in 100% oxygen, incremental doses of atracurium, and mechanical ventilation.

CPB was conducted using a roller pump with minimum occlusion to avoid hemolysis. Albumin was added in the prime solution for coating the CPB circuit to prevent the initiation of the complement cascade. Intermittent warm, bold cardioplegia was given every 20 minutes. The temperature was maintained 32-34˚c during bypass. Blood pressure was maintained around 70 mmHg. Urine output was maintained with the use of mannitol 100ml and furosemide 20mg. Two units of Fresh-frozen plasma (FFP) and four units of platelets were given immediately after weaning from CPB. No antifibrinolytic agent such as tranexamic acid was used. Operative data included CPB, aortic cross-clamp, and operative time were recorded.

Postoperative:

Patients were transferred to ICU on a mechanical ventilator. Investigations were done to assess hemolysis; hemoglobin, hematocrit, reticulocyte count, bilirubin, urea, and creatinine. Fentanyl 2 um/kg/h was used for postoperative analgesia in the 1st 24 hours. Adrenaline, noradrenaline, and nitroglycerine were given according to hemodynamics, and amiodarone for atrial fibrillation (AF) control was used when needed. The standard protocol for postoperative fluid and blood transfusion was used for both groups of patients. Blood transfusion was used for patients with significant chest drainage associated with hemodynamic instability, when hemoglobin value less than 10 g/dL with associated symptoms related to anemia, or when hemoglobin value less than 8 g/dL.

Total drainage in chest drains in 24 hours was recorded, and the number of blood units required postoperatively was recorded.

Our protocol for the management of G6PD deficient patients includes avoidance of drugs listed in Table 1 and Table 2.

Table 1: Drugs to be avoided for G6PD deficient patients [13]

Drugs to be avoided for G6PD deficient patients, Bubp et al., 2015 [13]	
Dapsone	Phenazopyridine
Flutamide	Primaquine
Furazolidone	Rasburicase
Isobutyl nitrite	Nitrofurantoin
Methylene blue	Phenazopyridine
Niridazole	Primaquine

Endpoints

The primary endpoints were postoperative hemoglobin value, hematocrit percent, bilirubin level, reticulocyte count, creatinine, and blood urea immediate postoperative and in the first seven days postoperative. The secondary endpoints were ventilation time, and total drainage in chest drains in 24 hours. The postoperative complications and outcome, including ICU stay and total hospitalization time, were also recorded.

Statistical analysis:

All statistical analyses were done using IBM SPSS for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). According to the type of data, qualitative data represented as number and percentage and quantitative data represented by means ± standard deviation (SD). Quantitative variables were compared using a t-test or Mann–Whitney test if not normally distributed, and qualitative variables were compared using the Chi-square test or Fischer's Exact test if the frequency of the events is less than 5. P-value was set at <0.05 for significant results.

Results

Males represent 80% of G6PD deficient patients. There were no significant differences between the G6PD deficiency group and the control group regarding age, sex, NYHA functional class, and comorbidities (diabetes mellitus, and chronic obstructive pulmonary disease). (table 3). No preoperative differences between both groups regarding hemoglobin level, hematocrit percent, blood urea, and serum creatinine (p = 0.086, 0.092, 0.192 and 0.098 respectively), while there

Table 2: Drugs to be used with caution in therapeutic doses for G6PD deficient patients [13]

Drugs to be used with caution in therapeutic doses for G6PD deficient patients, Bubp et al., 2015 [13]		
Acetaminophen	Chloroquine	Sulfacytine
Acetylsalicylic acid	Colchicine	Sulfadiazine
Antazoline	Diphenhydramine	Sulfaguanidine
Antipyrine	Glyburide	Sulfamethoxazole
Ascorbic acid: IV doses only reported	Isoniazid	Sulfisoxazole
Benzhexol	L-Dopa	Trimethoprim
Chloramphenicol	Quinine	Tripelennamine
Chlorguanidine	Streptomycin	Vitamin K

Table 3: Preoperative data in both groups

Variables	G6PD deficiency Group (n = 20)	Control Group (n = 20)	P
Age, y	52.0±6.77	51.6±5.85	0.843
Male sex, n (%)	16 (80%)	14 (70%)	0.465
NYHA FC			
I	5 (25%)	4 (20%)	0.500
II	6 (30%)	6 (30%)	0.634
III	7 (35%)	8 (40%)	0.500
IV	2 (10%)	2 (10%)	0.697
WHO Class			
I	3 (15%)	-	
II	10 (50%)	-	
III	7 (35%)	-	
DM	13 (65%)	12 (60%)	0.743
COPD	5 (25%)	4 (20%)	0.500
Hemoglobin (g/dl)	13.84±1.4	14.46±0.6	0.086
Hematocrit (%)	41.1±4.1	42.94±2.2	0.092
Total Bilirubin(mg/dl)	1.03±0.33	0.57±0.11	<0.001
Reticulocyte (%)	1.87±0.62	0.54±0.18	<0.001
Urea (mg/dl)	16.8±3.4	15.5±2.8	0.192
Creatinine(mg/dl)	1.01±0.12	0.94±0.14	0.098

NYHA FC = New York Heart Association Functional Class, WHO Class = World Health Organization G6PD deficiency Class, DM = diabetes mellitus, COPD = chronic obstructive pulmonary disease

were significant elevations in preoperative total bilirubin and reticulocytes in G6PD deficient patients (p <0.001, for both). (Table 3)

Operative results

CABG was done for 40% of G6PD deficient patients with a mean of 2.5±0.8 graft per patient. LIMA to LAD was done for all patients in both groups. Valve surgery was done for 60% of G6PD deficient patients. Mitral valve repair was done for four patients in the G6PD deficiency group versus two patients in the control group. Valve replacement with mechanical valve prosthesis was done for replacing mitral and aortic valves in the rest of the patients.

Table 4: Operative data of both groups

Variables	G6PD deficiency Group (n = 20)	Control Group (n = 20)	P
Type of surgery			
CABG	8(40%)	8(40%)	0.626
Graft/patient	2.5±0.8	2.4±0.8	0.694
Valve Surgery	12 (60%)	12 (60%)	0.626
AVR	3 (15%)	3 (15%)	
AVR+MVR	1 (5%)	1 (5%)	
MV Repair	2 (10%)	2 (10%)	
MVR	2 (10%)	2 (10%)	
MVR+TV Repair	4 (20%)	4 (20%)	
ACC time(min)	68.3±10.5	64.6±12.2	0.239
CPB time(min)	125.6±15.4	115.9±23.5	0.132
Operative time(min)	171.4±49.9	156.8±42.4	0.401

CABG = coronary artery bypass grafting, AVR = Aortic valve replacement, MVR = Mitral valve replacement, TV = Tricuspid valve, ACC = Aortic-cross clamp, CPB= Cardiopulmonary bypass.

There were no significant differences between both groups regarding the type of surgery, aortic-cross clamp time, CPB time, and total operative time. (Table 4)

Postoperative results

G6PD deficient patients had significantly lower hemoglobin levels (HB) and hematocrit values (HCT) at all the six days post-operation. In the 7th postoperative day, there were no significant differences between both groups, but their values did not reach the preoperative levels. (Table 1,Table 5)

G6PD deficient patients had significantly higher total bilirubin (TB) and reticulocytes at all the seven days post-operation. At the same time, the differences between both groups regarding urea and creatinine levels were not significant all the time. (Table 6,Table 7)

Ventilation time was significantly higher in G6PD deficient patients than control patients (10.3±2.7 Vs. 8.2±1.9 hours, P = 0.01). Also, drainage volume was significantly more in G6PD deficient patients than control patients (750.1±136.6 Vs. 532.5±154.1 mL, P <0.001). The need for blood transfusion was more in G6PD deficient patients (1.9±1.4 Vs. 0.8±1.0 unit/patient, P <0.001). The maximal and the minimal partial pressure of arterial oxygen (Max PaO2 and Min PaO2) in ICU were significantly lower in G6PD deficient patients (P <0.001 and P <0.001 respectively). ICU stay, and hospital stay was longer in G6PD deficient patients than control patients (p = 0.004 and P <0.001, respectively). (Table 8)

In both groups of patients, there was one case of mortality in the G6PD deficiency group, a patient suffering from rheumatic severe aortic incompetence and severe mitral incompetence with low ejection fraction (EF = 34%), aortic and mitral valve replacement was done for him. The patient could not be weaned from CPB due to left ventricular failure.

Discussion

Glucose-6- phosphate dehydrogenase deficiency is a genetic X-linked recessive disorder that occurs almost exclusively in males. The usual clinical presentations are the consequences of hemolysis that include anemia, jaundice, hepatosplenomegaly, and reticulocytosis [7]. In hexose monophosphate pathway of glucose metabolism, G6PD reduce nicotinamide adenine

Table 5: Postoperative HB level and hematocrit value for both groups

Variables	G6PD deficiency Group (n = 19)	Control Group (n = 20)	P
HB g/dL			
Immed. PO	10.1±0.57	10.5±0.45	0.021
1st_POD	9.44±0.94	10.0±0.59	0.036
2nd_POD	9.84±0.76	10.48±0.47	0.003
3rd_POD	9.56±0.48	10.74±0.65	0.004
4th_POD	9.81±0.87	11.08±0.58	<0.001
5th_POD	10.5±1.14	11.2±0.59	0.028
7th_POD	10.91±1.39	11.2±0.41	0.397
Hematocrit (%)			
Immed.PO	30.3±2.33	32.1±2.12	0.016
1st_POD	28.1±3.31	30.1±2.79	0.047
2nd_POD	28.4±2.15	30.6±2.25	0.003
3rd_POD	28.6±1.67	30.7±1.99	0.001
4th_POD	29.5±1.79	31.2±2.01	0.008
5th_POD	31.6±1.97	33.2±1.37	0.005
7th_POD	32.8±3.93	31.72±1.53	0.401

HB = hemoglobin, Immed.PO= Immediate postoperative, POD = postoperative day, HCT = hematocrit

Table 6: Postoperative total bilirubin and reticulocytes for both groups

Variables	G6PD deficiency Group (n = 19)	Control Group (n = 20)	P-value
T Bilirubin(mg/dl)			
Immed.PO	1.37±0.39	1.02±0.31	0.004
1st_POD	1.51±0.51	0.98±0.45	0.002
2nd_POD	2.06±0.69	0.91±0.35	<0.001
3rd_POD	2.24±0.75	0.85±0.24	<0.001
4th_POD	1.91±0.63	0.76±0.19	<0.001
5th_POD	1.51±0.51	0.67±0.15	<0.001
7th_POD	1.21±0.40	0.63±0.15	<0.001
Reticulocyte (%)			
Immed.PO	1.74±0.57	0.59±0.19	<0.001
1st_POD	1.85±0.51	0.57±0.13	<0.001
2nd_POD	2.05±0.63	0.62±0.202	<0.001
3rd_POD	2.22±0.72	0.57±0.19	<0.001
4th_POD	2.18±0.74	0.51±0.18	<0.001
5th_POD	2.08±0.73	0.55±0.18	<0.001
7th_POD	1.9±0.64	0.54±0.17	<0.001

T Bilirubin = Total Bilirubin, Immed.PO= Immediate postoperative POD = post-operative day

dinucleotide phosphate (NADP) to reduced nicotinamide adenine dinucleotide phosphate (NADPH). NADPH reduces oxidized glutathione to reduced glutathione, which protects cells from oxidative damage. Deficiency in G6PD leads to a decrease in reduced glutathione production, which will not be enough to protect cells from oxidative stress that will be very critical in the case of red blood cells due to the absence of mitochondria [3-5].

The two standard tests for diagnosis of G6PD deficiency are the Beutler test and the quantitative spectrophotometric analysis test. The rapid Beutler fluorescent spot test detects the generation of NADPH from NADP. Failure of the blood spot to fluoresce under ultraviolet light indicates a positive test.

Table 7: Postoperative blood urea and serum creatinine for both groups of patients

Variables	G6PD deficiency Group (n = 19)	Control Group (n = 20)	P-value
Urea (mg/dl)			
Immed.PO	18.2±5.08	20.6±5.41	0.160
1st_POD	20.9±3.82	22.1±4.62	0.380
2nd_POD	22.3±4.08	23.1±3.71	0.527
3rd_POD	19.8±4.14	20.6±3.57	0.525
4th_POD	19.4±4.28	21.2±4.05	0.187
5th_POD	22.3±7.71	20.0±3.65	0.248
7th_POD	18.9±4.47	19.7±2.72	0.515
Creatinine(mg/dl)			
Immed.PO	1.08±0.13	1.11±0.15	0.509
1st_POD	1.07±0.18	1.11±0.06	0.375
2nd_POD	0.94±0.07	1.0±0.21	0.235
3rd_POD	0.91±0.06	0.95±0.18	0.352
4th_POD	0.90±0.08	0.95±0.17	0.249
5th_POD	0.86±0.11	0.9±0.14	0.326
7th_POD	0.82±0.07	0.85±0.06	0.161

Immed.PO= Immediate postoperative POD = post-operative day

Table 8: Intensive care (ICU) and ward data of both groups

Variables	G6PD deficiency Group (n = 19)	Control Group (n = 20)	P
Ventilation time(hr.)	10.3±2.7	8.2±1.9	0.01
Max PaO_2 (mm Hg)	410.7±20.0	461.2±15.2	<0.001
Min PaO_2 (mm Hg)	67.0±6.9	89.0±12.8	<0.001
Drainage volume(mL)	750.1±136.6	532.5±154.1	<0.001
Blood Transfusion (Unit/patient)	1.9±1.4	0.8±1.0	<0.001
ICU stay (days)	3.1±0.87	2.3±0.71	0.004
Hospital stay (days)	8.7±1.41	6.0±1.02	<0.001
Mortality	1 (5%)	0	0.50

hr. = hours, Max PaO_2 = maximal partial pressure of arterial oxygen, Min PaO_2= minimal partial pressure of arterial oxygen, ICU = intensive care unit

The quantitative spectrophotometric analysis of G6PD activity in a leukocyte-depleted sample is considered as the standard quantitative test [3- 5, 14].

G6PD deficient patients are very sensitive to oxidative stress when exposed to certain precipitating medications, certain foods, certain chemicals, infection, and extracorporeal circulation [10, 15,16].

CPB has mechanical damaging factors (roller pumps, cardiotomy suction, and circuit tubes) and it potentiates systemic inflammation through the production of oxygen free radicals, both can result in red cell lysis and endothelial injury. These effects are exaggerated in G6PD deficient patients due to their high sensitivity to oxidative stress [3, 11,12]. Although Altikat and colleagues [17] in an in-vitro study reported that isoflurane, sevoflurane, diazepam, and midazolam had an inhibitory effect on G6PD activity, there is no sufficient in-vivo research data supporting this concept. On the other hand, anesthetic agents like isoflurane, sevoflurane, fentanyl, and rocuronium were used safely in G-6-PD deficiency patients [3,11,18,19], and our experience supports this view.

The free radical scavengers such as mannitol and allopurinol can minimize the free radical generation by decreasing the effect of oxidative stress on the cells [6, 20, 21]. Our protocol for managing G6PD deficiency patients in this study included the use of mannitol and allopurinol as free radical scavengers. Chowdhry and collaborators [11] and Kumar [3] used the same strategy.

Mannitol has an osmotic diuretic effect and free radical scavenging properties that can reduce the extent of ischemic injury [22]. Besides, the main usage of allopurinol is to compete with the enzyme xanthine oxidase needed for uric acid formation; it can decrease the oxidative stress through free radical scavenging [23].

G6PD deficient patients may suffer from renal impairment from free hemoglobin release that can lead to blockage of renal tubules [3, 6, 8, 14]. One of our strategies for the preparation of patients for operation is to maintain good urinary flow using IV mannitol and Furosemide in the day before the operation to avoid renal tubular injury due to free hemoglobin.

Careful workup in the perioperative period to minimize factors that would cause oxidative stress, such as infection, inflammatory response, ischemia, low flows on CPB, hypothermia was our main strategy for this sector of patients.

Our results demonstrated that lower postoperative hemoglobin levels and hematocrit values with more need for blood transfusion and higher postoperative total bilirubin and reticulocytes in G6PD deficient patients indicating more hemolysis of red cells in those patients as compared to the control group of patients without G6PD deficiency. Also, G6PD deficient patients in

the study had lower levels of Max PaO2 and Min PaO2 and longer ventilator time, indicating more liability to hypoxia. The above results are consistent with the results of Gerrah and coworkers [12] who compared the postoperative parameters of G6PD deficient patients undergoing cardiac surgery using CPB with a control group, and they demonstrated that the G6PD deficiency group had longer ventilator duration, more hypoxia and increased hemolysis with more need to blood transfusion. Chowdhry and collaborators [11] reported mitral valve replacement using CPB for a 38 years old male patient that had G6PD deficiency with an uneventful intraoperative and postoperative course. They use mannitol and allopurinol as free radical scavengers. Kumar [3] presented a 30-year-old lady suffering from G6PD deficiency, severe mitral stenosis, and severe mitral regurgitation with moderate tricuspid regurgitation. Mitral valve replacement and tricuspid annuloplasty using CPB was done for her with an uneventful intraoperative and postoperative course using a strategy to minimize hemolysis that depends on quick surgery, maintenance of normothermic bypass and maintaining good urine output. Tas and coworkers [7] in a case report of aortic valve replacement for a known G6PD deficient patient, a 16-year-old suffering from severe aortic incompetence as a result of endocarditis, they reported that open-heart surgery could be applied safely in patients with G6PD with careful perioperative management. Ramadass and colleagues [24] performed a bidirectional Glenn (BDG) procedure with atrial septectomy for a G6PD deficient boy who had a ventricular septal defect (VSD) and double outlet right ventricle (DORV) under CPB. They used mannitol to scavenge free radicals and avoid acidosis by adding sodium bicarbonate to the prime solution with an uneventful outcome. The mortality in G6PD deficiency patients in our study was 5%, which we consider as an acceptable rate for this category of patients.

Limitations

The main limitation is the retrospective nature of the study with small sample size. However, this study design is accepted to study rare conditions.

Conclusion

Despite the management strategy, G6PD deficient patients undergoing cardiac surgery are more liable to hemolysis and hypoxia with more need for blood transfusion and longer ventilation time, ICU, and hospital stays when compared to patients with normal G6PD enzyme activity. Further research to improve the outcomes in G6PD deficient patients is required.

Conflict of interest: Authors declare no conflict of interest.

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