

N-Acetyl Cysteine (NAC): Can it be useful in G6PD deficiency patient undergoing cardiac surgery

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Abstract

Background: A 45yrs old male known diabetic and G6PD deficiency had coronary triple vessel disease and undergoing cardiac bypass surgery. There is history of hemolytic episodes following drug intake for febrile illness on and off since childhood. **Case Presentation:** On preoperative evaluation, patient had jaundice with Total bilirubin-2.4 mg/dl, direct bilirubin-0.5 mg/dl, indirect bilirubin-1.9mg/dl and Hb-12.3 gm% with all other investigations within normal limits. Patient premedicated with Inj.pantoprazole(iv), Inj.glycopyrrolate and Inj.tramadol intramuscularly. Cefoperazone + Sulbactam 1.5g was given as prophylactic antibiotic. Anaesthesia was induced with Inj.propofol, fentanyl. Tracheal intubation facilitated with Inj.Atracurium and anaesthesia maintained with O₂/Air mixture, Atracurium+ Fentanyl infusion. Intraoperative monitoring included ECG, invasive BP (radial, femoral), pulmonary artery pressure, pulse oximetry, temperature, EtCO₂ and urine output. The patient was started with NAC infusion @ 6ml/kg/hr after skin incision and continued up to extubation. Patient was hemodynamically stable throughout the surgery with minimal inotropic support. Post operatively patient constantly observed for complications of hemolysis. On second post operative day patients peripheral smear showed anisocytosis with hypochromic microcytes, elevated bilirubin levels(T-3.2, D-0.3, I-2.9), reticulocyte count 2%, Hb-11g%, LDH-425. Quantitative analysis of G6PD enzyme showed 3.7. Patient discharged on fourth post operative day with Hb-11.4 and decreased bilirubin levels (T-1.8, D-0.3, I-1.5). On 10th post operative day during followup visit, patient was anicteric without any symptoms. **Conclusion:** Administration of NAC during surgery helps in early recovery with minimal complications and reduced need of blood transfusion in G6PD deficient patients.

Key Word: N-Acetyl Cysteine.

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INTRODUCTION

The G6PD enzyme is part of the pentose monophosphate shunt which catalyses the oxidation of glucose-6-phosphate and reduction of NADP⁺ to NADPH. NADPH

maintains glutathione in its reduced form, as a scavenger for oxidative metabolites. The pentose monophosphate shunt is the only source for NADPH in RBC. Therefore, deficiency of G6PD enzyme makes RBCs more susceptible to oxidative stress from certain drugs, metabolic conditions, infections etc. Patients undergoing cardiac surgeries are exposed to perioperative ischemia, reperfusion injury, hypoperfusion, hypothermia, extra corporeal circulation and acidosis¹ leading to increased production of free radicals². Individuals, depending on the level of G6PD enzyme activity manifest the extent of hemolysis. Perioperative administration of free radical scavengers³, avoiding drugs causing oxidative stress and maintaining optimal hemodynamics may reduce the postoperative hemolysis. Studies have shown NAC, the n-acetyl derivative of the amino acid L-cysteine either

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directly as a free radical scavenger or indirectly detoxify reactive metabolites through facilitation of glutathione synthesis. This intrinsic property made us use NAC in our G6PD deficient patient to minimize oxidative stress on RBCs.

CASE REPORT

A 45yrs old male known diabetic came with complaint of chest pain and breathlessness for 6 months. Coronary angiography showed triple vessel disease with Ejection Fraction (EF) -30%. Off pump CABG was planned. Patient was diagnosed with G6PD deficiency 10yrs before during evaluation for jaundice. There is history of hemolytic episodes following drug intake for febrile illness on and off since childhood and had blood transfusion once. On preoperative evaluation, patient had jaundice with Total bilirubin-2.4 mg/dl, direct bilirubin-0.5 mg/dl, indirect bilirubin-1.9mg/dl and Hb-12.3 gm% with all other investigations within normal limits. Patient premedicated with Inj.pantoprazole(iv), Inj.glycopyrrolate and Inj.tramadol intramuscularly. Cefoperazone + Sulbactam 1.5g was given as prophylactic antibiotic. Anaesthesia was induced with Inj.propofol, fentanyl. Tracheal intubation facilitated with Inj.Atracurium and anaesthesia maintained with O₂/Air mixture, Atracurium+ Fentanyl infusion. Intraoperative monitoring included ECG, invasive BP (radial, femoral), pulmonary artery pressure, pulse oximetry, temperature, EtCO₂ and urine output. Sulphydryl group donor, N-acetyl Cysteine, Nikorandil and soda bicarbonate infusions were given intra operatively upto extubation. The patient was started with NAC infusion @ 6ml/kg/hr after skin incision and continued upto extubation. Patient was hemodynamically stable throughout the surgery with minimal inotropic support. Post coronary perfusion ABG showed pH-7.49, pCO₂-28.9, pO₂-122, HCO₃-21.8, BE (-0.4), SaO₂-99% and Hb-10.8gm%. Total duration of surgery was 3 hours 40 minutes. Approximate intraoperative blood loss was 250ml and urine output 300ml. Total intravenous fluid infused was RL 1000ml+ starch 500ml. Post operatively patient shifted to CTSICU. Patient investigated for hemolysis: peripheral smear-normal, reticulocyte count 2%. One unit whole blood transfused. Patient electively ventilated for 5hrs and then extubated after check ABG. On second post operative day patients peripheral smear showed anisocytosis with hypochromic microcytes, elevated bilirubin levels(T-3.2, D-0.3, I-2.9), reticulocyte count 2%, Hb-11g%, LDH-425. Quantitative analysis of G6PD enzyme showed 3.7. Patient discharged on fourth post operative day with Hb-11.4 and decreased bilirubin levels (T-1.8, D-0.3, I-1.5). All investigation done to check the occurrence of hemolysis has been shown in table 1.

Table 1: Investigations of this patient to check occurrence of hemodialysis

	Pre op	Intra op	0 POD	2 th POD	4 th POD
Hb	12.3	10.8	12.3	11.0	11.4
Peripheral smear			WNL	Microcytic hypochromic	
Retic count			2%	2%	
T Bilirubin	2.5			3.2	1.8
Direct Bilirubin	0.2			0.3	0.3
Indirect Bilirubin	2.3			2.9	1.5
LDH				425	

Patient was discharged on 4thpost operative day with improvement in hemoglobin level and decreased bilirubin levels. There was no necessity for blood transfusion. On 10thpost operative day during followup visit, patient was anicteric without any symptoms. Therefore hemolysis in our patient post surgery was limited with early recovery.

DISCUSSION

G6PD deficiency is an X-linked recessive disorder, where males usually manifest the abnormality and females are carriers. Specific G6PD alleles are associated with G6PD variants with different enzyme levels and thus different degrees of clinical disease severity. The variation in G6PD levels accounts for differences in sensitivity to oxidants. According to WHO classification this patient belonged to G6PD class III variant with enzyme level of 3.7U/g Hg. Class III patients exhibit self limiting acute episodic hemolytic anaemia due to oxidative stress induced by exposure to certain drugs including anaesthetic agents. From the study done by Altikat *et al.*, they have concluded that isoflurane, sevoflurane, diazepam and midazolam have an inhibitory effect on G6PD activity in vitro⁴. In a review article, Elyssi and Rowshan⁵ suggest to avoid drugs which cause methemoglobinemia like lignocaine in G6PD deficient patients. Therefore these drugs were avoided and rest of the drugs administered in a graded dosage fashion though there is no any document supporting their inhibitory activity⁵. This patient underwent off pump coronary artery bypass grafting surgery, which not only reduces oxidative stress and inflammation but also reduces the risk of blood loss caused by hemolysis and need for transfusions⁶.

Administration of N-acetyl cysteine (NAC), an excellent source of sulphhydryl group, precursor in the synthesis of glutathione, a direct free radical (hydroxyl, hypochlorous acid) scavenger and inflammation modulator was considered for this patient. Historically NAC has been used as a mucolytic agent in respiratory illnesses; however it appears to also have beneficial effects in conditions characterized by oxidative stress, such as HIV infection, cancer, heart disease and cigarette smoking⁷. NAC also

reduces methemoglobin level in G6PD deficiency as suggested by Wright RO *et al.* in their in vitro study. These properties of NAC favoured its administration to reduce oxidative injury and subsequent hemolysis. The patient was started with NAC infusion @ 6ml/kg/hr after skin incision and continued up to extubation. Patient was hemodynamically stable throughout the surgery with minimal inotropic support. Blood sugar levels and ABG done at regular intervals were normal. General anaesthesia typically masks the immediate signs of hemolysis, making it difficult to identify a hemolytic crisis. Even hypotension, which could be a result of hemolysis, may be attributed to other causes in an anesthetized patient. Vigilant monitoring of patient's vitals to recognize signs of hemolysis and removal of offending agent is what expected in the management of G6PD deficient patient. Most patients with G6PD deficiency are not anaemic, but episodes of intravascular hemolysis and consequent anaemia can be triggered by oxidative stress. Clinical signs and symptoms of hemolysis typically arise within 24 to 72hrs of drug dosing and anaemia can worsen until about day seven. Our patient had fall in hemoglobin on 2nd post op day with elevated indirect bilirubin, but LDH remained normal. Clinical manifestation was only in terms of jaundice with stable hemodynamic parameters. Acute hemolysis is self-limiting to 8-14 days as new RBCs produced to compensate anaemia contain high levels of G6PD and are not vulnerable to oxidative stress. But in rare instances it can be severe enough to warrant a blood transfusion. Signs and symptoms of hemolytic crisis include cyanosis, headache, dyspnea, fatigue, lumbar/substernal pain, jaundice, dark urine. Therefore follow up of patient post operatively for ongoing hemolysis is necessary. Patient was discharged on 4th post operative day with improvement in hemoglobin level and decreased bilirubin levels. This suggests early recovery without hemolytic complications in the patient and there was no necessity for blood transfusion. N-Acetyl cysteine can be

effective in preventing hemolytic complications in patients undergoing cardiac bypass surgery.

On above discussion we can conclude following point:

- Factors determining the outcome in G6PD deficient patients undergoing cardiac surgery are – the quantity of G6PD enzyme and the extent of oxidative stress.
- Oxidative stress should be minimized by avoiding drugs which are contraindicated and also any kind of insult which triggers free radical release.
- Free radical scavenger like NAC can be considered to further decrease hemolysis due to oxidative stress.
- Further randomized controlled studies with NAC in G6PD deficient patient are necessary to establish its usefulness.

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