Automated-red cell exchange for methaemoglobinaemia in a G6PD-deficient patient

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ABSTRACT

Methaemoglobinaemia in G6PD deficiency can be managed by oxidizing agents such as methylene blue and red cell exchange (RCE). We describe a G6PD-deficient patient who presented with oxidative stress with methaemoglobinaemia and was successfully managed with automated-RCE. At presentation, the patient had anaemia, was restless, was tired and had dyspnoea. Co-oximetry showed methaemoglobinaemia of 10.1 U/g. Further testing revealed the patient had insufficient quantities of G6PD enzyme activity (0.1 U/g Hb). In view of methaemoglobinaemia, severe G6PD deficiency and signs of haemolysis, therapeutic RCE was planned. The patient underwent two automated-RCE procedures on consecutive days, bringing down his methaemoglobin levels from 12.5 to 0.1 U/g. In each procedure, 1.5 volumes of RCE at 100% balance rate was performed using 5 units of red blood cells. The patient responded well to RCE and other supportive treatment and was off medication and doing well at day 100 of follow-up.

Natl Med J India 2020;33:149–51

INTRODUCTION

The prevalence of G6PD deficiency varies from 2.9% to 7.5% in different geographical areas.[1] In India, the prevalence has been reported from 0% to 27% in different caste, ethnic and linguistic groups.[2] The disease is initially detected in the neonatal period, early childhood and sometimes even in adults. The disease commonly presents as acute haemolysis as a result of oxidative stress due to infection, drugs or both. Patients are usually managed symptomatically. Management includes prevention of further oxidative exposure to patients, oxygen support and red blood cell (RBC) transfusion for anaemia, phototherapy and exchange transfusion for raised total serum bilirubin. G6PD deficiency is sometimes complicated with the emergence of methaemoglobinaemia. Although methaemoglobinaemia is managed by an oxidizing agent such as methylene blue, these cannot be used in patients with G6PD deficiency;[3,4] instead, red cell exchange (RCE) is indicated.[5] We present an adult male with G6PD-deficiency who presented with oxidative stress, complicated by methaemoglobinaemia and was successfully managed with automated-RCE.

THE CASE

A 36-year-old, known G6PD-deficient, male, born to non-consanguineous parents, presented with fever, chills and headache for 7 days and haematuria for 1 day. He had been evaluated elsewhere and been found to have malaria (*Plasmodium vivax*) and was started on artesunate and primaquine. The patient did not respond to treatment and was referred to us in view of his deteriorating condition. His mutational analysis report for G6PD deficiency was not available. History of fava beans ingestion was absent.

At presentation, the patient had anaemia (haemoglobin 5.8 g/dl) along with leucocytosis (total leucocyte count 36.24×10^3/cmm), restlessness, fatigue, dyspnoea and air hunger. On the basis of the presenting complaints and past history, the patient was admitted to the intensive care unit and started on intravenous (i.v.) fluids, i.v. antibiotics and other supportive measures. His oxygen saturation on the pulse oximeter was between 75% and 80%, and arterial blood gas showed saturation above 90%. Co-oximetry resolved this mismatch and confirmed methaemoglobinaemia of 10.1 U/g. On further testing, the patient had insufficient quantities of G6PD enzyme activity on assay (0.1 U/g Hb; reference 4.6–13.5 U/g Hb). A provisional diagnosis of methaemoglobinaemia in G6PD-deficient state class II (according to the WHO classification) was made, and the patient started on high-flow nasal oxygen therapy.

Other biochemical investigations revealed deranged liver function tests (LFTs): raised bilirubin and liver enzymes (bilirubin 8.8 mg/dl; serum glutamic oxaloacetic transaminase [SGOT] 9615 U/L; serum glutamic pyruvic transaminase [SGPT] 2825 U/L; gamma-glutamyl transferase 223 U/L) and normal kidney function tests (creatinine 1 mg/dl). The patient's lactate dehydrogenase enzyme (19 504 U/L) was raised, but both direct and indirect Coombs tests were negative. High-performance liquid chromatography revealed no haemoglobinopathies, and normal coagulation profile ruled out disseminated intravascular coagulopathy. Severe haemolysis in the patient was inferred due to oxidative stress caused by infection, antimalarial drugs or both. Haemolysis was aggravated due to the underlying G6PD deficiency.

For the first 48 hours after admission, the patient was maintained only on medical management and non-invasive ventilation (biphasic positive airway pressure system); however, in view of the worsening methaemoglobinaemia (12.5 U/g), severe G6PD deficiency (0.1 U/g Hb) and signs of ongoing haemolysis on peripheral smear, the primary treating physician and transfusion medicine specialist planned therapeutic RCE.

The automated-RCE procedure was done using a haemodialysis-type double-lumen 16 F catheter inserted in the left femoral vein for unhindered blood flow. The procedure was performed on the apheresis machine Com.Tec (Fresenius Kabi, Germany) using the standard PL1 kit (Fresenius Kabi, Germany). The machine has an in-built software programme for performing RBC exchange (primarily for sickle cell disease). The same programme was applied for this patient. At the onset, demographic details of the patient including gender (male), weight (65 kg) and height (172 cm) along with haematocrit (Hct 26%) were entered in the software as a part of pre-procedural requirements; the machine calculated the total blood volume (4.56 L) and total red cell volume (1.1 L) of the patient.

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The patient underwent two RCE procedures on consecutive days. The first procedure resulted in improvement in both clinical and laboratory parameters; methaemoglobinaemia decreased from 12.5 to 8.1 U/g and air hunger decreased. Hence, the treating team decided to perform a second procedure in a bid to wean the patient off assisted ventilation. Post-second procedure, the oxygen saturation improved further: 85%–90% to 90%–95% after the first and to 95%–100% after the second exchange procedures and methaemoglobinaemia reduced to 0.1 U/g.

To perform 1.5 volumes of RCE at 100% balance rate and target Hct of 25%, the machine calculated the volume of RBCs to be exchanged as 1510 ml and 1500 ml, respectively, for the two procedures. Each procedure used 5 units of RBC. Hct of each RBC bag was measured just before the initiation of RCE. The volume and Hct of each RBC bag were entered in the 'RBC calculator' of software for RCE (Version 04.03.08, Com. Tec, Fresenius Kabi, Germany). All RBC units utilized for RCE were within 7 days of donation and leucoreduced. The mean volume and Hct of bags used for the first and second procedures were 304 ml and 57% and 300 ml and 58%, respectively.

The patient's vital parameters including pulse rate, blood pressure, oxygen saturation and respiratory rate were monitored before, during and after the procedure. Continuous i.v. calcium gluconate 10% (20 ml in 80 ml normal saline) infusion at the rate of 60 ml/hour was given to the patient during the procedures to prevent citrate effect. The two procedures lasted for a mean of 79 minutes and were uneventful.

During the hospital stay, 7 units of RBC, 4 units of random donor platelet concentrate and 1 unit of single-dose platelet concentrate were transfused to the patient besides the 10 units of RBC used in the RCE procedures. The patient responded well to RCE and other supportive treatment and was shifted out of the ICU on day 10 with improved LFT (bilirubin 1.8 mg/dl, SGOT: 86 U/L and SGPT 228 U/L), increased platelet count (338 000/cmm), no haematuria and maintenance of oxygen saturation on room air. The patient was discharged on day 12. The patient was off medication and was well at day 100 of follow-up.

DISCUSSION

Prevalence

G6PD deficiency is common, affecting around 400 million people worldwide and is characterized by considerable biochemical and molecular heterogeneity.[6] It is due to a genetic defect caused by mutations in the G6PD gene, and its inheritance shows a typical X-linked pattern with higher incidence in males than females.[7] In humans, G6PD gene is affected by almost 140 different mutations and most of them are missense point mutations. The prevalence of G6PD deficiency varies in different geographical areas with lower frequency in the Americas (3.4%), Europe (3.9%) and the Pacific (2.9%) compared to Asia (4.7%), Middle East (6.0%) and sub-Saharan Africa (7.5%).[1] In India, the prevalence varies from 0% to 27% in different caste, ethnic and linguistic groups.[2] The most common mutation reported by Sukumar *et al*. was G6PD Mediterranean (60.4%) and G6PD Kerala–Kalyan (24.5%).[8] Mutation results in both decreased stability of the enzyme and qualitative changes in enzyme. The WHO classifies G6PD deficiency into five classes on the basis of G6PD enzyme activity as percentage of normal.[9] Our patient was classified as class II as his enzyme activity was <10% with intermittent haemolysis.

Pathophysiology of G6PD deficiency

G6PD is important in red cell metabolism and its deficiency renders the red cell extremely vulnerable to any kind of oxidative stress.[10] G6PD catalyses the first step in hexo-mono-phosphate (HMP) shunt. Nicotinamide adenine dinucleotide phosphate (NADPH) produced by HMP shunt maintains reduced glutathione (GSH). GSH is essential for protecting red cells from oxidative damage. Therefore, a G6PD-deficient patient lacks the ability to protect RBCs against oxidative stress. Most G6PD-deficient patients are asymptomatic. However, oxidative stress from drugs (some antimalarial, chemotherapeutic agents, sulphonamides, antipyretics, analgesics, etc.), infections and ingestion of fava beans can result in acute haemolysis due to inadequate 'energy currency' in the cell due to the deficiency of G6PD enzyme.[6] In our patient, the deficiency of G6PD enzyme exaggerated the acute onset haemolysis and concomitant methaemoglobinaemia due to the infection (malaria) and subsequent ingestion of primaquine.

This haemolysis in acquired G6PD deficiency is intravascular and usually results in normocytic and normochromic anaemia. Patients usually compensate, at least milder cases (WHO class III), by increased erythrocyte production as evident by increased reticulocyte count.[11] Newer erythrocytes produce relatively more G6PD enzyme and can resolve this oxidative stress by producing more NADPH.[12]

Diagnosis

Blood smear is an important tool for the diagnosis of G6PD deficiency as its results are rapidly available and a provisional diagnosis can be made. Further, a blood smear can suggest the diagnosis of G6PD deficiency even if a G6PD assay is normal, as may be found after acute haemolysis in G6PD-deficient patients. A typical blood smear in an appropriate clinical setting is an indication to repeat the assay once the acute haemolytic episode is over.[13] On presentation, our patient had a high reticulocyte count (3.5%) and the peripheral smear was described as normocytic normochromic with polychromasia and 4 nucleated RBCs per 100 white blood cells. Clinically, the patient was decompensated with severe deficiency of G6PD and acute onset of haemolysis.

G6PD assay is another important test used for quantification of enzyme activity. The test can help classify males as either normal or deficient hemizygotes and females as either normal homozygotes or heterozygotes with 'intermediate' enzyme activity or deficient homozygotes. For adults, the International Council for Standardization in Haematology suggests the normal range for G6PD activity values to be 8.83±1.59 U/g Hb at 30 °C.[12]

Management

In a G6PD-deficient patient with ongoing haemolysis, an important and critical part of management is removal of the oxidative exposure. For example, either stop the oxidative stress-inducing drug or treat the infection that is causing oxidative stress resulting in haemolysis. In our patient, the likely cause of methaemoglobinaemia with severe haemolysis was oxidative stress caused by the infection, the antimalarial drug (primaquine) or both and aggravated by G6PD deficiency. Hence, the patient was started on artesunate (safe for G6PD-deficient patients) and was discontinued after the malarial results were negative. If a G6PD-deficient patient also develops methaemoglobinaemia, the treatment of choice for methaemoglobinaemia is debatable—methylene blue or RCE.

Few published reports recommend the administration of methylene blue starting at a lower dose of 0.3–0.5 mg/kg and titrating upwards as the first-line treatment in G6PD-deficient patients with life-threatening methaemoglobinaemia.[14,15] However, we decided against methylene blue and performed RCE because first, methylene blue is itself an oxidizing agent and would have further increased oxidative stress. Second, methylene blue would have resulted in the loss of NADPH required to produce reduced GSH because of the utilization of NADPH for the reduction of methylene blue itself.[3,4,16] Thus, methylene blue was avoided in the patient because the administration of methylene blue could have theoretically worsened the haemolytic anaemia and therefore RCE was done.

RCE removes the defective RBCs and replaces them with healthy donor RBCs. The amount of RBC to be replaced is calculated based on the amount of defective RBCs to be removed or the amount of defective RBCs left at the end of the procedure. Although the in-built software is designed to perform RCE for acute complications in sickle cell disease, the same principle was applied to perform RCE in this patient with methaemoglobinaemia. Moreover, our hypothesis that exchanging 50% of patients' G6PD-deficient RBCs with fresh donors' RBCs would provide adequate benefit and response in patients proved correct.

RCE could be manual or automated. Compared to manual RCE, automated-RCE is easier, quicker and more effective. It achieves haematological targets quickly and consistently.[5,17] There are reports on the utility of RCE in patients with methaemoglobinaemia caused by drugs, poisoning, etc.[4,17] To the best of our knowledge, the present report is the first report from India of successful automated-RCE for methaemoglobinaemia in G6PD-deficient patients. This indication is not mentioned in the current ASFA guidelines.[18] Successful management of our patient as well as in other similar reports[17] makes a case for including 'RCE in methaemoglobinemia' as an indication in future ASFA guidelines.

Conflicts of interest. None declared

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