Letter to the Editor

Importance of rational use of vitamin C in G6PD deficiency patients

A case report

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Vitamin C (ascorbic acid) is not only a cofactor of 15 kinds of mammalian enzymes, but also an electron donor to detoxify free radical tissues in vivo, which plays a pharmacological role as an antioxidant [1]. There are two forms of vitamins, namely, ascorbic acid in the reduced state and dehydroascorbic acid (DHA) in the oxidized state. Vitamin C exhibits predominantly pro-oxidant activity by reducing Fe^{3+} to Fe^{2+} [2], leading to formation of superoxide and hydrogen peroxide, and followed by the formation of DHA. Thus, under some circumstances vitamin C will generate oxidants. In fact, DHA has been proposed as an indication of oxidative stress [3]. There have been reports of hemolysis after high dose vitamin C administration in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, but is uncommon [4]. We report here the first case of a male with G6PD deficiency, coexpressed with cholecystolithiasis and cholecystitis, who developed extreme hemolysis and hyperbilirubinemia after receiving rapid infusion of pharmacologic dose vitamin C.

A 27-year-old man with G6PD deficiency (he has been identified as a G6PD deficiency patient through clinical tests before) was referred to our hepatobiliary surgery because of cholecystolithiasis and cholecystitis. On the first day, inflammation biomarker ferritin (Fer) reached 3056 (ng/mL) [5]. The patient received fasting treatment, anti-infective therapy, and nutrition fluid supplementation. Cefmetazole Sodium (Harbin Pharmaceutical Group Pharmaceutical Factory) administered intravenously, 2 g two times a day. On the second day, 5% compound amino acid injection (18) (Guangdong Litai Pharmaceutical Co.,Ltd.) 250 ml and alanyl glutamine 10 g (Hainan Lionco Pharmaceutical Group Co.,Ltd.) iv one time a day and vitamin C 4 g, vitamin B6 400 mg and KCl 1 g in 5% glucoseand sodium chloride solution 250 ml was infused in about 20 minutes one time a day. On the third day, he began to appear with scleral jaundice. The red blood cell count and hemoglobin decreased from 3.12×10^{12}/L and 114.0 g/L to 2.93×10^{12}/L and 107.0 g/L respectively, total bilirubin, conjugated bilirubin and unconjugated bilirubin rose from 123.2 mmol/L, 29.6 mmol/L, 93.7 mmol/L to 923.4 μmol/L, 461.7 μmol/L, 249.8 μmol/L respectively. Liver function demonstrated: aspartate aminotransferase 133 U/L, alanine transaminase 274 U/L, γ glutamyl transferase 153 U/L, Urine studies showed black color, Uric bilirubin qualitative 3+, Uric bravery former qualitative 4+. Given the patient's initial presentation and laboratory studies, we can conclude that the jaundice abnormality was caused by obstructive jaundice at the time of admission, and the later extreme jaundice was caused by hemolytic jaundice which caused by G6PD deficiency related acute hemolysis. The patient was treated with steroids, hepatoprotective drugs [glutathione, (GSH) and other drugs] and folic acid and avoidance of agents with known hemolysis risk (such as vitamin C). Ultimately, the patient's symptoms from hemolytic jaundice improved, hemoglobin remained stable, and the patient was discharged 11 days later with an extensive list of medications (including vitamin C) to avoid because of G6PD deficiency.

Glucose-6-phosphate dehydrogenase (G6PD) is essential in the metabolism of glucose and catalyzes the rate-limiting step in the reduction of nicotineamide adenine dinucleotide phosphate (NADP) to NADPH. NADPH is used to convert GSSG (oxidised glutathione) to GSH (reduced glutathione) for protection against oxidative stress or oxidative attack [6]. The defense system that tackled oxidative stress in RBC was highly dependent on the activity of G6PD enzyme. Intact RBC have a high capacity antioxidant

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system because it contains all of the enzymes necessary for the NADPH biosynthesis [7, 8]. In most cases, in the steady state, the consequences of G6PD deficiency are not noticeable. The NADPH produced by the residual G6PD activity and by 6PGD activity is just enough to keep the erythrocyte going, with marginal reduction of its life span. However, if exogenous oxidative stress is applied, the production of NADPH in G6PD deficient RBC is not reduced enough, GSH stored in the cells is rapidly depleted, and various protein in RBC are destroyed, which eventually leads to cellular death. Therefore, a G6PD-deficient patient lacks the ability to protect RBC against oxidative stresses from ingestion of fava beans, certain drugs, metabolic conditions, and infections [9].

The RBC also have rapid and efficient vitamin C recycling mechanisms, which is a process of extracellular vitamin C oxidation to DHA, transported as DHA, intracellular reduction to vitamin C by cellular antioxidants, such as GSH, to maintain adequate tissue levels of vitamin C. In RBC of G6PD deficiency, DHA can accumulate intracellularly by autocrine recycling, inducing ROS and consuming GSH and ATP, inhibiting glycolysis and finally inducing cell death [10]. Inflammation could accelerate the oxidation burden of RBC in this process and infection is the most common cause of acute hemolysis in G6PD deficient subjects [11, 12]. Under physiological conditions, DHA concentrations are extremely low. However, extracellular vitamin C is massively oxidized to DHA in certain pathological conditions, such as certain drugs, infections, thus increasing its uptake and intracellular concentration in RBC [13].

Indeed, low-moderate dose intravenous vitamin C may be the treatment of choice for drug-induced hemolysis in patients with G6PD deficiency [2]. This can increase the reserve of redox capacity in the blood rather than red blood cells. The pharmacological action occurs in the serum rather than in the RBC, which vitamin C can scavenge plasma oxidative stressor [14–16]. The exact mechanism of high-dose vitamin C produced haemolysis in G6PD deficiency is uncertain but is thought to entail generation of H_2O_2 and other reactive oxygen species, which rapidly consume away the limited GSH supply of G6PD deficiency patients. Vitamin C possesses pro-oxidant properties at high pharmacologic concentrations which is used to use vitamin C as an anti-cancer therapeutic agent but not normal cells [17].

In our patient, 250 ml 5% glucose and sodium chloride solution of vitamin C 4 g, vitamin B6 400 mg and KCl 1 g was infused in about 20 minutes. This result resulted in a transient high concentration of vitamin C in serum. Vitamin C induce oxidative stress, depleted GSH was the last straw that overwhelmed RBC reducing power. Hemolysis typically occurs 24–72 hours after ingestion, with resolution within four to seven days. Hemolysis occurs after exposure to the oxidative stressor but does not continue despite continued infection or drug. This is thought to be a result of older RBC having the greatest enzyme deficiency and undergoing hemolysis first. The younger RBC that typically have higher levels of enzyme activity are able to sustain the oxidative damage without hemolysis [18, 19]. Our patient's experience was fully in line with this process. The above information suggest that in the pharmacological dosage vitamin C should not be considered contraindicated in patients with G6PD deficiency, but it should not be infused quickly in order to avoid short-term high-concentration vitamin C. Clinicians should bear in mind the possibility that vitamin C exposure may result in hemolysis in patients with G6PD deficiency.

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Conflict of interest
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