Intravascular hemolysis and methemoglobinemia from high dose vitamin C

Ryan K. Nelson[1], Janet Ma[2], Niloofar Latifi[3], Rebecca E. Sell[1*]

European Journal of Medical Case Reports
Volume 4(2):49–51

https://doi.org/10.24911/ejmcr/173-1544044604

ABSTRACT

Background: Vitamin C is often used by complementary and alternative medicine practitioners for its antioxidant properties. We describe a case of severe hemolytic anemia and methemoglobinemia paradoxically resulting from an oxidative stress of high dose vitamin C in a patient with previously undiagnosed glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Case Presentation: A 47-year-old man presented with severe hemolytic anemia and methemoglobinemia days after receiving 395 g of intravenous (IV) vitamin C at an alternative medicine practice. He was managed conservatively with transfusions and his hemolysis subsided after several days. His G6PD level, measured months after his presentation, was deficient at 0.4 units/g.

Conclusion: While vitamin C is often considered an antioxidant, its utilization in tissues produces its oxidized form (dehydroascorbic acid) which depletes intra-erythrocyte stores of glutathione. Patients with G6PD deficiency have reduced abilities to restore intracellular glutathione, placing them at risk for oxidative stress, and subsequent hemolysis that can be life threatening.

Keywords: Case report, hemolysis, methemoglobinemia, vitamin C, glucose-6-phosphate dehydrogenase deficiency.

Received: 06 December 2018 **Accepted:** 10 December 2019

Type of Article: CASE REPORT **Specialty:** Toxicology

Funding: This work was not supported by any grant or other forms of funding.

Declaration of conflicting interests: The authors declare that there is no conflict of interests regarding the publication of this case report.

Correspondence to: Rebecca E. Sell
*Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, University of California San Diego, La Jolla, CA.
Email: rsell@ucsd.edu
Full list of author information is available at the end of the article.

Background

Vitamin C is often used by complementary and alternative medicine practitioners for its antioxidant properties. We describe a case of severe hemolytic anemia and methemoglobinemia paradoxically resulting from an oxidative stress of high dose intravenous (IV) vitamin C in a patient with previously undiagnosed glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Case Presentation

A 47-year-old Puerto Rican male presented to the Emergency Department with 2 days of progressive shortness of breath and jaundice occurring two weeks after being diagnosed with oropharyngeal squamous cell carcinoma. Despite recommendations from his oncologist to consider traditional chemotherapy, our patient sought treatment from an alternative medicine provider and was provided with three days of a modified version of Myers' Cocktail. While Myers' Cocktail typically contains 2–5 ml magnesium chloride hexahydrate 20%, 1–3 ml calcium gluconate 10%, 1,000 mcg hydroxocobalamin (vitamin B12), 100 mg pyridoxine hydrochloride (vitamin B6), 250 mg dexpanthenol (vitamin B5), 1 ml B complex 100, and 4–20 mL of 222 mg/ml vitamin C administered as an IV infusion [1], our patient's modified version contained added amounts of vitamin C totaling 395 g in escalating doses (65 g on day 1, 130 g on day 2, and 200 g on day 3). The 3-day infusion was completed one day prior to symptom onset and 3 days prior to his presentation to the hospital. The patient was on no other medications. He had previously received and tolerated vitamin C infusions at significantly lower doses (consistent with doses of a typical Myers' Cocktail) but had never attempted such a high dose regimen.

On presentation, our patient was afebrile and tachycardic with oxygen saturations of 82%–85%. His skin was jaundiced with cola-colored urine and his arterial blood sample was dark purple (Figure 1). Laboratory findings were notable for a hemoglobin of 7.4 g/dl (baseline 13. 8 g/dl, Figure 2), LDH of 1492 units/l (normal 25–175 units/l), and indirect bilirubin of 5.6 mg/dl (normal <1.2 mg/dl) consistent with an intravascular hemolytic anemia.

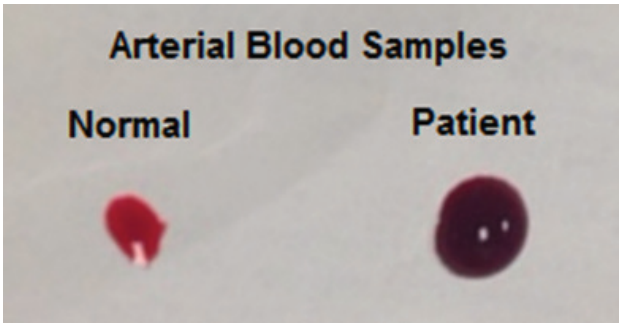

Figure 1. *Arterial blood sample.*

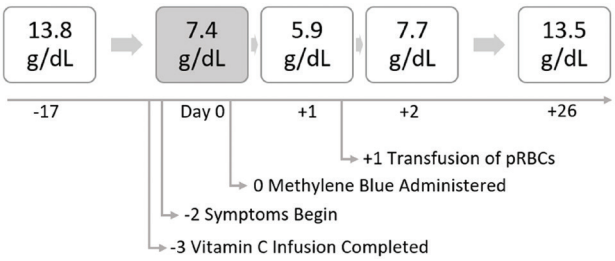

Figure 2. *Hemoglobin values in relation to events surrounding presentation to the hospital. Day 0 signifies day of admission.*

His reticulocyte count suggested an adequate bone marrow response. There was no evidence of blood loss and a peripheral smear and Coombs test did not demonstrate microangiopathic or autoimmune phenomenon. Given the low oxygen saturations and dark blood, his methemoglobin concentration was measured at 7.1%. He received a 1 mg/kg dose of methylene blue with a subsequent drop in both his hemoglobin concentration (7.4 g/dl to 5.9 g/dl) and methemoglobin fraction (7.1% to 3.0%) over the next 12 hours (Figure 2). While Vitamin C was identified as a potential culprit from patient history, a plasma concentration was not obtained at a time in the patient's course when vitamin C would still be expected to be present. Then, managed conservatively with intravenous fluids and blood transfusions, his hemolysis eventually resolved over several days. While his G6PD level was 4.6 units/g in the setting of active hemolysis and multiple blood transfusions, repeat testing several months after the event came back deficient at 0.4 units/g. The patient reported no known previous episodes of hemolysis and was counseled on his enzyme deficiency, including avoidance of select medications.

Discussion

This case highlights the potential for severe hemolysis with methemoglobinemia in a patient with previously undiagnosed G6PD deficiency supplementing with high doses of vitamin C. Few case reports have demonstrated this previously [2,3] and recent *in vitro* studies have provided insight for a possible underlying mechanism [4]. While vitamin C is often considered an antioxidant, its utilization in tissues produces its oxidized form (dehydroascorbic acid) which can rapidly deplete intra-erythrocyte stores of glutathione when present in high concentrations [4,5]. These stores are typically replenished by shunting glucose down the pentose phosphate pathway [4,5], but patients with G6PD deficiency are limited in this ability to the degree that their G6PD concentrations are reduced. It is, therefore, plausible that oxidation of hemoglobin and erythrocyte membrane proteins ensues and the result is methemoglobin formation and subsequent hemolysis from the loss of cellular integrity. In our patient, the use of methylene blue potentially exacerbated the hemolysis by acting as an oxidant in the absence of sufficient NADPH.

Conclusion

While several case reports have demonstrated success in treating methemoglobinemia with high doses of vitamin C when methylene blue was either contraindicated [6] or unavailable [7], this case suggests that such practice may need to be used with caution. It is noteworthy, however, that the patient described above was exposed to approximately tenfold the amount of vitamin C used in these studies. Nevertheless, high doses of vitamin C are being increasing used by complementary and alternative medicine practitioners and its potential for life-threatening consequences should not go overlooked.

What is new?

Only a few, old case reports have described severe hemolysis resulting from vitamin C. We describe this phenomenon in a patient with previously undiagnosed glucose-6-phosphate dehydrogenase deficiency taking unusually high doses of vitamin C. It further links the case to a mechanism based on recent in vitro studies.

Acknowledgments

The authors would like to thank the patient for allowing us to produce a manuscript of his case.

List of Abbreviations

IV	Intravenous;
G6PD	Glucose-6-Phosphate Dehydrogenase

Consent for publication

The patient described in this case report provided written consent to the inclusion of material pertaining to themselves in manuscript publication.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

Author details

Ryan K. Nelson[1], Janet Ma[2], Niloofar Latifi[3], Rebecca E. Sell[1]

1. Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, University of California San Diego, La Jolla, CA, United States of America
2. Department of Medicine, University of California San Diego, La Jolla, CA, United States of America
3. Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, United States of America

References

1. Gaby AR. Intravenous nutrient therapy: "the Myers' Cocktail". Altern Med Rev. 2002;7(5):389–403.
2. Mehta JB, Singhal SB, Mehta BC. Ascorbic-acid-induced haemolysis in G-6-PD deficiency. Lancet. 1990;336(8720):944. https://doi.org/10.1016/0140-6736(90)92317-B
3. Rees DC, Kelsey H, Richards JD. Acute haemolysis induced by high dose ascorbic acid in glucose-6-phosphate dehydrogenase deficiency. BMJ. 1993;306(6881):841–2. https://doi.org/10.1136/bmj.306.6881.841
4. Zhang ZZ, Lee EE, Sudderth J, Yue Y, Zia A, Glass D, et al. Glutathione depletion, pentose phosphate pathway

activation, and hemolysis in erythrocytes protecting cancer cells from vitamin C induced oxidative stress. J Biol Chem. 2016;291(44):22861–7. https://doi.org/10.1074/jbc.C116.748848
5. Wilson JX. The physiological role of dehydroascorbic acid. FEBS Lett. 2002;527(1–3):5–9. https://doi.org/10.1016/S0014-5793(02)03167-8
6. Reeves DJ, Saum LM, Birhiray R. I.V. ascorbic acid for treatment of apparent rasburicase-induced methemoglobinemia in a patient with acute kidney injury and assumed glucose-6-phosphate dehydrogenase deficiency. Am J Health-Syst Pharm. 2016;73(9):e238–42. https://doi.org/10.2146/ajhp150591
7. Lee KW, Park SY. High-dose vitamin C as treatment of methemoglobinemia. Am J Emerg Med. 2014;32(8):936. https://doi.org/10.1016/j.ajem.2014.05.030

Summary of the case

1	**Patient (gender, age)**	Male, 47
2	**Final diagnosis**	Glucose 6-Phosphate Dehydrogenase Deficiency; Hemolysis from Vitamin C; Methemoglobinemia
3	**Symptoms**	Jaundice
4	**Medications**	Vitamin C (High Dose)
5	**Clinical procedure**	Transfusions
6	**Specialty**	Internal Medicine; Critical Care