

Vitamin C-induced Hemolysis: Meta-summary and Review of Literature

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ABSTRACT

Vitamin C is increasingly being used, and even high doses are considered safe. However, complications including hemolysis have been reported. We performed a systematic search from PubMed, Science Direct, and Google Scholar databases from January 1975 till July 31, 2021. Search terms used were "Vitamin C" OR "ascorbic acid" AND "haemolysis" OR "haemolytic anaemia." Data regarding patient's demographics, outcomes and dose, duration, and form of vitamin C were extracted. Fourteen case reports matched the selected criteria, with age ranging from 3 weeks to 75 years with 78.6% being males. About 71.4% were diagnosed to have glucose-6-phosphate dehydrogenase (G6PD) deficiency but previous hemolysis was reported in only two patients, and 57.1% were prescribed vitamin C for nutritional supplementation. The dose ranged from 1 to 200 g/day with 57.1% receiving intravenous formulations. Half of these patients developed other complications including acute kidney injury (AKI), disseminated intravascular coagulation, oxalosis, and methemoglobinemia. About 78.6% developed complications within 3 days of starting vitamin C and only one death was reported. Vitamin C is generally a safe drug but it should be prescribed with caution and only when benefits outweigh the risks. Physicians should be aware of potential complications like severe hemolysis and AKI, especially when using high doses and in G6PD deficiency.

Keywords: Ascorbic acid, Hemolysis, Hemolytic anemia, Vitamin C.

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INTRODUCTION

Recent years have witnessed the expanding use of high-dose vitamin C in the management of critically ill patients with sepsis, acute respiratory distress syndrome (ARDS), cancer, and even severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia.¹⁻⁴ Vitamin C or ascorbic acid has been explored in the treatment of sepsis and septic shock because of its antioxidant properties, scavenging free radicals, and postulated bacteriostatic effect.¹ Besides, working as an enzyme cofactor for many important biological reactions, vitamin C has other proposed mechanism of actions including the prevention of mitochondrial dysfunction and septic cardiomyopathy, regulating macrophage function, and preservation of macro- or microvascular function.^{1,5} Moreover, because of its potential anti-inflammatory and immune-enhancing properties, its therapeutic role has expanded well beyond the treatment of scurvy and promoted even in healthy individuals as "immune-booster".⁵ Vitamin C is a water-soluble vitamin and is generally considered safe to use even in higher doses. Although no serious side effects have been reported in trials evaluating the effectiveness of high-dose vitamin C, safety was not the primary endpoint of these trials. Various case reports have reported several side effects with vitamin C ranging from interference with laboratory tests to life-threatening acute kidney injury (AKI).^{6,7} Here, we aimed to evaluate hemolysis associated with the use of high-dose vitamin C reported in various case reports over the past several decades.

MATERIALS AND METHODS

We performed a systematic search for this meta-summary from PubMed, Science Direct, and Google Scholar databases from January 1, 1975, till July 31, 2021. The search terms used were

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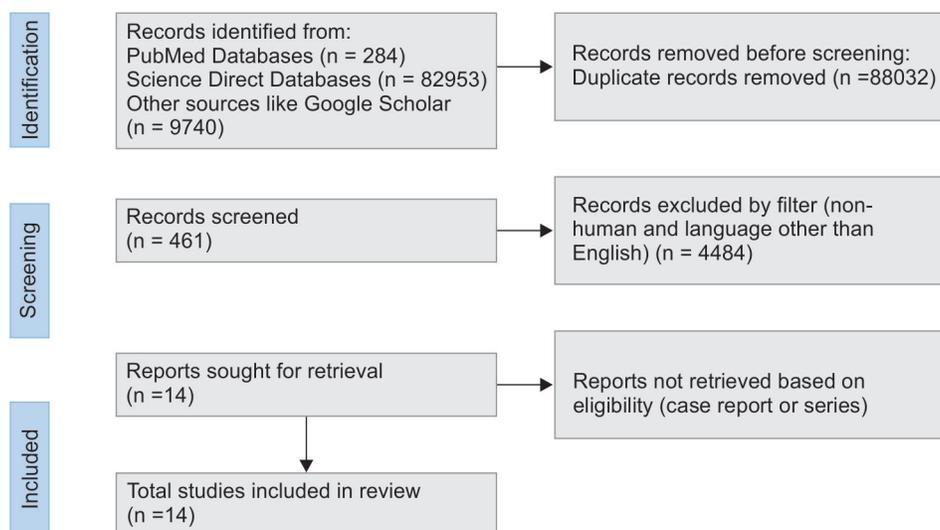
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"Vitamin C" OR "ascorbic acid" AND "hemolysis" OR "hemolytic anemia." The inclusion criteria were (1) published case reports or case series with individual patient details and (2) a documented history of recent vitamin C use and objective evidence of acute hemolysis related to it. Further, it was filtered for the literature published in the English language and humans. The authors screened all the search results to include only the relevant literature. Duplicate articles from different search databases were excluded. All the authors further reviewed eligible studies for final inclusion based on the availability of individual patient data (Flowchart 1).

All the case reports and case series were evaluated, and the data were extracted for the patient's demographics, dose, duration, formulation of vitamin C therapy, and patient outcomes. A datasheet for evaluation was further prepared for descriptive analysis.

Flowchart 1: PRISMA flow diagram of the selected literature for the meta-summary

RESULTS

A total of 14 case reports matched the selected criteria, with publications ranging from 1975 to 2020. Half of the publications were from the Asian Continent. The age of the patients ranged from 3 weeks to 75 years with male predomination (78.6%, 11/14). About 71.4% (10/14) were diagnosed with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and in two reports, G6PD deficiency was not reported. A previous history of hemolysis was reported in only two patients (14.3%). The main indication of prescribing vitamin C was nutritional supplementation in 57.1% of patients. Other indications included sepsis (two patients), cancer therapy (two patients), treatment of rheumatoid arthritis, and hemifacial spasm (one patient each) (Table 1).^{8–20}

The dose of vitamin C received by these patients ranged from 1 g/day up to 200 g/day. The 3-week-old infant received a dose of 30 mg/day orally. About 57.1% of patients received intravenous formulations of vitamin C, but a substantial number (42.9%) also developed hemolysis after receiving oral formulation. Half of these patients also developed other complications, including AKI, disseminated intravascular coagulation (DIC), oxalosis, and methemoglobinemia, with AKI being the most common associated complication found in 42.9% of cases. A great majority, 78.6% (11/14), of patients developed these hemolytic complications within 3 days of starting the vitamin C therapy. Only one death (7%) was reported in these case reports, but there was a significant associated morbidity (Table 1).^{8–20}

DISCUSSION

The present meta-summary showed that hemolysis might be precipitated after the administration of high-dose intravenous vitamin C, especially in the presence of G6PD deficiency. Oral vitamin C, if consumed in large doses for a prolonged period, may also cause hemolysis. Males are generally affected, which may be attributed to a higher incidence of G6PD deficiency. All age groups may be affected, and most of the cases occur within 72 hours of the initiation of therapy. AKI is a commonly associated complication along with acute hemolysis. Deposition of heme pigment in the renal tubules leads to cell injury and death, causing AKI. Even

though most of the patients were discharged alive, there was a significant associated morbidity, and rarely, it could be fatal.

Vitamin C is increasingly used for varied clinical conditions. High doses of intravenous vitamin C have been evaluated, with doses up to 100 g/day used to manage critically ill patients.¹ The reported side effects are rare and generally mild. These include interference with laboratory tests, lethargy/fatigue, phlebitis, renal stones, hyperglycemia, hyponatremia, muscle cramps, nausea, vomiting, headache, altered mental status, syncope, hemolysis, and AKI.^{6,7} However, specific patient populations like those with underlying renal dysfunction and G6PD deficiency may be at higher risk of developing complications. The polypharmacy in critically ill patients and popular belief on the benign nature of vitamin C may have caused under-recognition and under-reporting of side effects.

G6PD deficiency is the most prevalent enzyme deficiency, with almost 5% of the world population (more than 329 million) affected. As it is an X-linked recessive disorder, males are generally affected and may develop severe clinical consequences. Most of the patients remain asymptomatic. Hemolytic anemia, secondary to infections or exposure to oxidizing agents/medications, is the most common clinical presentation in adults.²¹ The incidence of G6PD deficiency varies in different regions of the world and different ethnicities. African Americans and Asians are more likely to have G6PD deficiency, and the most widely affected regions of the world include Africa, the Middle East, and Asia.²¹

Vitamin C is considered an antioxidant and has been used to manage hemolysis associated with oxidative damage in patients with G6PD deficiency.²² However, it is postulated that it may lead to oxidative stress and hemolysis when used in higher doses. Ascorbic acid is converted in the tissues into its oxidized form, dehydroascorbic acid, which may diminish the intraerythrocyte glutathione stores, especially when present in high concentrations as may be the case when high doses of vitamin C are prescribed. In G6PD deficiency, these glutathione stores are not replenished, leading to oxidative damage and resultant hemolysis.²³

These side effects have been generally associated with using high doses of vitamin C. However, “high dose” is not clearly defined and is arbitrarily considered a dose of more than 10 g/day in adults.²⁴ Although most of the cases in the present meta-summary had taken

Table 1: General parameters, complications, and outcomes of patients with vitamin C hemolysis

Case No.	Year of publication	Country of origin	Age (in years)	Sex	G6PD deficiency	History of hemolysis	Clinical indication	Dose (g/day)	Formulation	Complications	Duration in days of therapy before hemolysis	Final outcome
1	1975	USA	68	M	Yes	None	Sepsis/burns	80	IV	AKI, DIC	2	Death
2	1988	Canada	3 weeks	F	None	None	Supplement	30 mg	Oral	None	2	Alive
3	1990	India	10	M	Yes	None	Supplement	4	Oral	None	1	Alive
4	1990	India	10	M	Yes	None	Supplement	4	Oral	None	1	Alive
5	1993	UK	32	M	Yes	None	Supplement	80	IV	AKI	2	Alive
6	1994	Japan	24	M	None	Yes	Supplement	NR	Oral	None	NR	NR
7	1994	Japan	67	M	NR	Yes	Supplement	NR	Oral	None	NR	NR
8	2011	UK	29	F	NR	None	Supplement	1	Oral	AKI and secondary oxalosis	30	Alive
9	2014	Taiwan	9 months	M	Yes	None	Sepsis	12	IV	None	2	Alive
10	2017	USA	59	M	Yes	None	Rheumatoid arthritis	75	IV	AKI, methemoglobinemia and oxalosis	0	Alive
11	2018	Australia	54	M	Yes	None	Cancer	60	IV	AKI	2	Alive
12	2018	China	27	M	Yes	None	Supplement	4	IV	None	3	Alive
13	2019	USA	47	M	Yes	None	Cancer	65–200	IV	Methemoglobinemia	3	Alive
14	2020	Hong Kong	75	F	Yes	None	Hemifacial spasm	30	IV	AKI	2	Alive

G6PD, glucose-6-phosphate dehydrogenase; USA, United States of America; UK, United Kingdom; IV, intravenous; AKI, acute kidney injury; DIC, disseminated intravascular coagulation; NR, not reported; M, male; F, female

“high dose” of intravenous vitamin C,^{8,11,15–17} we also found cases reported after prolonged low-dose oral vitamin C,¹⁴ and even after low-dose intravenous therapy.^{9,10,18}

Strength and Limitations

This is the first meta-summary evaluating hemolysis associated with vitamin C therapy. We aimed to make the physicians aware of this possible complication, especially when prescribing high-dose vitamin C. This meta-summary encompassed all the case reports published in the last five decades and tried to identify the risk factors associated with this complication. This meta-summary is limited by a small number of case reports available for analysis. In addition, different criteria were used for the diagnosis of hemolysis in case reports and the incidence of side effects could not be ascertained as we had included data from case reports and not trials. The included studies were only case reports, with a considerable reporting bias, missing data, and hence, the results cannot be generalized.

CONCLUSION

Vitamin C administration is generally safe, but like any other drug, it should be prescribed with caution and only when benefits outweigh any side effects. Physicians should be aware of potential complications like severe hemolysis and AKI, which may be precipitated when using high doses of vitamin C, especially in patients with G6PD deficiency. These complications generally occur early after the initiation of therapy. Hence, utmost care and monitoring for these complications in the first 72 hours is suggested.

HIGHLIGHTS

Use of high-dose vitamin C may lead to complications like hemolysis and AKI, especially in patients with G6PD deficiency. These complications may occur within 72 hours of the initiation of intravenous or oral therapy.

CONTRIBUTORS

DJ involved in concept, design, literature search, clinical studies, data acquisition, data analysis, statistical analysis, guarantor, manuscript preparation, manuscript editing, and manuscript review; RJ involved in literature search, clinical studies, data acquisition, data analysis, statistical analysis, and manuscript review; PN involved in data analysis, statistical analysis, manuscript editing, and manuscript review.

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