Hemorrhage associated with vitamin C deficiency in surgical patients

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Background. *Diffuse hemorrhage in surgical patients with normal coagulation parameters may be caused by vitamin C deficiency and is rapidly reversed by vitamin C replacement.*
Methods. *Patients treated on a surgical service were entered into a clinical registry over a 12-month period if they experienced diffuse hemorrhage in the face of normal coagulation parameters and a plasma ascorbic acid level < 0.6 mg/dL (normal 0.6-2.0 mg/dL). Oral vitamin C replacement was administered after determination of plasma ascorbic acid level. Response to therapy, including subsequent bleeding events, need for blood transfusions, and demographic data including social and dietary history were retrospectively reviewed from hospital and outpatient clinic records.*
Results. *Twelve patients with bleeding diatheses and low plasma ascorbic acid levels were identified. Plasma ascorbic acid levels were 0.1 to 0.5 mg/dL (mean, 0.3 mg/dL). There were 6 men and 6 women; age ranged from 46 to 90 years (mean, 78 years). Coagulation parameters were normal in all patients. Diffuse postoperative bleeding from nonsurgical causes was evident in 10 of 12 patients. Four patients, 2 of whom had operations, presented with chronic recurrent blood loss from the gastrointestinal tract. Each patient received 250 to 1000 mg of vitamin C replacement daily. Within 24 hours of vitamin C administration, there was no further evidence of clinical bleeding nor need for subsequent blood transfusions in any patient.*
Conclusions. *Vitamin C deficiency should be included in the differential diagnosis of nonspecific bleeding in surgical patients. Prolonged hospitalization, severe illness, and poor diet create vitamin C deficiency with significant clinical consequences. Oral vitamin C replacement rapidly reverses the effects of this disorder. (Surgery 2002;131:408-12.)*

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VITAMIN C DEPLETION, or scurvy, was first described in 1500 BC. The clinical manifestations of this disorder, including hemorrhage, were well described in the 1600s by physicians caring for Dutch and British sailors who were subject to dietary deficiencies on long sea voyages. The classic experiments with the use of citrus fruits to prevent scurvy in British sailors performed by James Lind in 1753 were the first controlled clinical trials ever reported. The recognition that fresh fruits and vegetables prevented scurvy, along with improved diets and vitamin supplementation, has made vitamin C depletion a rare entity. However, relative vitamin C deficiency has recently been shown to be much more common than previously believed, especially in those that are socially isolated, elderly, or critically ill, as well as in impoverished individuals, fad dieters, and patients undergoing dialysis.[1] Clinical consequences of vitamin C deficiency, including hemorrhage, have been reported in patients with plasma ascorbic acid levels less than 0.6 mg/dL.[1] We hypothesized that diffuse, non-surgical bleeding in patients with normal coagulation parameters may be caused by vitamin C deficiency and is rapidly reversed by vitamin C replacement.

METHODS

Gundersen Lutheran Medical Center is a 350-bed tertiary referral hospital with a general surgery residency serving 19 counties in southwestern Wisconsin, southeastern Minnesota, and northeastern Iowa. Patients treated on a surgical service were entered into a clinical registry over the 12-month period ending May 2000 if they experienced diffuse hemorrhage in the face of normal coagulation parameters and had a measured plasma ascorbic acid level < 0.6 mg/dL. The cause, evaluation, and treatment of hemorrhage were recorded in each case. Patients with a surgical or other identifiable source of bleeding were excluded from analysis.

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Coagulation parameters studied included international normalized ratio, partial thromboplastin time, fibrinogen level, and platelet count. The vast majority of patients with diffuse hemorrhage had identifiable abnormalities of coagulation that were able to be corrected. Only those patients with continued diffuse hemorrhage and normal coagulation parameters underwent measurement of ascorbic acid levels. Plasma ascorbic acid level was measured by high performance liquid chromatography with a normal range of 0.6 to 2.0 mg/dL. In each case, oral vitamin C replacement therapy was administered after the plasma ascorbic acid level had been drawn. Response to therapy, including subsequent bleeding events, serum hemoglobin levels, and the need for blood transfusions, was recorded. Demographic data, past medical history, and social history, including dietary habits, marital status, living situation, and tobacco and ethanol use were retrospectively reviewed from inpatient hospital charts and outpatient clinic records.

RESULTS

Twelve consecutive patients with bleeding diatheses and low plasma ascorbic acid levels were identified during the 12-month study period. Clinical characteristics of these 12 patients are shown in the Table. There were 6 men and 6 women. Ages ranged from 46 to 90 years (mean, 78 years). Ten (83%) patients were over 65 years of age. Plasma ascorbic acid levels were 0.1 to 0.5 mg/dL (mean, 0.3 mg/dL). Coagulation parameters were normal in all patients. Five patients were admitted to the General Surgery service; 4 underwent abdominal procedures; and 1 with a contained duodenal ulcer perforation was managed without operation. Four patients had undergone cardiovascular surgical procedures. One neurosurgical patient developed excessive bleeding from the scalp incision during a planned suboccipital craniotomy. The bleeding was diffuse, could not be controlled, and resulted in terminating the procedure. The remaining 2 patients were admitted for chronic, recurrent blood loss from the gastrointestinal tract. Of the 12 patients, 10 developed diffuse hemorrhage during or after the surgical procedures. Blood transfusions in the 12 patients ranged from 2 to 13 units (mean, 4.8 units) within 1 to 14 days of vitamin C deficiency recognition.

Seven patients had well documented poor oral nutrition or were receiving nothing by mouth. Five patients were receiving total parenteral nutritional replacement with multivitamin supplement at the time of the bleeding event. Seven patients lived alone, and 2 were nursing home residents. None of the 12 patients were smokers, and 3 had documented excessive ethanol use. One patient was receiving chronic hemodialysis.

After serum ascorbic acid levels were drawn, each patient received 250 to 1000 mg of vitamin C replacement daily. Within 24 hours of vitamin C administration, there was no further evidence of clinical bleeding, serum hemoglobin levels stabilized or increased, and there was also no need for subsequent blood transfusion in any patient. No patient received fresh frozen plasma or cryoprecipitate.

During the study period, 4 patients with diffuse hemorrhage and normal coagulation parameters and in whom plasma ascorbic acid levels were normal (0.6 to 0.9 mg/dL) were identified. Vitamin C was administered to 2 of these 4 patients. Clinical bleeding was never able to be controlled in 2 of these patients (1 had received vitamin C), and a third was lost to follow-up.

DISCUSSION

Ascorbic acid, or vitamin C, was originally identified by King and Waugh in 1932.[2] It is a stable, odorless, white solid that is water-soluable. It is readily absorbed from the gastrointestinal tract and excreted by the kidneys into the urine. Vitamin C is an essential nutrient in human beings and some other animals. Human beings, monkeys, guinea pigs, rainbow trout, Coho salmon, red vented bulbul, and Indian fruit-eating bats lack the enzyme L-gulonolactone oxidase needed in the final conversion of glucose to ascorbic acid. Thus, an obligatory dietary source of vitamin C is needed to maintain body stores in these species.

Vitamin C has many known biologic functions. It serves as an enzyme or cofactor for many biochemical reactions, the best understood being collagen cross-linking. In the production of collagen by the fibroblast, vitamin C is needed as a coenzyme for the proper hydroxylation of proline and lysine residues of procollagen. In the absence of sufficient levels of vitamin C, collagen is not hydroxylated, which creates an unstable, uncrosslinked, nonhelical configuration. Such collagen lacks tensile strength and is susceptible to enzymatic degradation. Vitamin C is also required for carnitine biosynthesis in muscle and neurotransmitter synthesis, including dopamine and serotonin. Furthermore, vitamin C is involved in cholesterol degradation and iron absorption. It has been shown to have immune-enhancing anticarcinogenic, and antioxidant effects.

The average-sized human being has a total body pool of 20 mg/kg of vitamin C, or about 1500 mg.[2]

Table. Clinical characteristics of 12 patients with vitamin C deficiency

Patient	*Age/ sex*	*Plasma ascorbic acid level*	*Social History*	*Relevant comorbid cconditions*	*Admission diagnosis*	*Surgical procedure*	*Nutrition*
1	78/F	.1	W, I	—	Pancreatic carcinoma	Pancreatoduodenectomy	TPN, TF
2	90/F	.3	W, I	—	Oral hemorrhage, hematuria	Teeth extractions	p.o.
3	72/M	.1	M	1 month s/p, CABG ×6	Upper GI bleed	Oversew duodenal ulcer	TPN poor p.o.
4	74/F	.5	NH	1 month s/p, cystectomy, ileal loop	Sepsis	None	TPN, TF
5	82/M	.2	W, I	Chronic anemia, ataxia	Cerebellar tumor	Suboccipital craniotomy (aborted)	p.o.
6	74/F	.1	W, I	Hemodialysis	Perforated diverticulitis	Colectomy, colostomy	TPN, p.o.
7	63/M	.5	M	—	Angina fatigue	CABG, AVR	p.o.
8	46/M	.4	D, I	—	Angina	CABG	p.o.
9	90/F	.3	NH	Chronic steroids	Perforated duodenal ulcer	None	Poor p.o.
10	73/M	.1	M	—	Syncope	CABG, AVR	Prolonged NPO
11	66/M	.4	I	—	Angina	CABG	TPN
12	78/F	.5	W, I	—	GI bleed	None	Prolonged NPO

Normal ascorbic acid range 0.6-2.0 mg/dL. *INR*, International normalized ratio; *PTT*, partial thromboplastin time; *W*, widow, widower; *I*, independent living; *TPN*, total parenteral nutrition; *TF*, enteral tube feeds; *EGD*, esophagogastroduodenoscopy; *BID*, twice a day; *p.o.*, oral intake; *q.d.*, every day; *M*, married; *s/p*, status postoperative; *CABG*, Coronary artery bypass grafting; *NH*, nursing home; *NA*, not available; *RBC*, red blood cell; *D*, divorced; *UGI*, upper gastronitestinal radiographic series; *AVR*, aortic valve replacement; *NPO*, no oral intake.

The average serum half-life of vitamin C is 16 to 20 days. Complete cessation of oral intake of vitamin C produces clinical signs of deficiency in 1 to 3 weeks.[1] The earliest symptoms of vitamin C deficiency include fatigue and anemia.[3] Other manifestations include poor wound healing, arthralgias, ataxia, and cardiac dysfunction. Vitamin C depletion occurs 2 to 3 months after the cessation of ascorbic acid intake.[1,2,4] Vitamin C depletion is manifested clinically as scurvy, with ecchymoses, bleeding gums, corkscrew hairs, follicular hyperkeratosis, myalgias, arthralgias, and death. Various laboratory tests are available to assess a person's ascorbic acid pool. The most widely accepted method is the plasma ascorbic acid assay, which uses high performance liquid chromatography.[1]

Important sources of dietary vitamin C include citrus fruits, green vegetables, peppers, tomatoes, berries, and potatoes. Meat, fish, poultry, eggs, and fortified dairy products contribute lesser amounts. All foods lose significant amounts of active vitamin C with cooking, canning, and extended shelf life. It has been stated that 10 mg per day of vitamin C is necessary to prevent full-blown adult scurvy.[5] This figure, and the Recommended Daily Allowance (RDA) of 60 mg for adults and 100 mg for smokers and pregnant women, was based upon data published in 1989.[3] The RDA translated to 5 servings of fruits or vegetables per day. A recent publication by Levine et al[6] has proposed that 100 mg to 200 mg per day of vitamin C for adults is a more appropriate dose. The higher daily requirement generated larger body stores to act as a buffer in preventing vitamin C deficiency. Levine and associates also alluded to the epidemic nature of vitamin C deficiency in the general population.[6] Their study showed that 25% of men and 33% of women surveyed ingested less than 2.5 servings of fruits and vegetables per day. Furthermore, 20% to 30% of adults in the United States were shown to ingest less than the 60 mg RDA of vitamin C. A similar study published by Johnston and Corte[7] confirmed these findings: 80% of adults surveyed consumed fewer than 2 servings of fruits and vegetables per day, and 10% consumed none at all.[7] They documented "marginal vitamin C status" in 24% of men and 18% of women in whom plasma ascorbic acid levels were randomly obtained. Sixteen percent of college students studied by Johnston et al[8] were also found to be vitamin C deficient.

Characteristics of those individuals particularly at risk for developing vitamin C deficiency include advanced age, living alone, tobacco use, heavy ethanol consumption, psychiatric disturbances and fad dieting.[1,2,9,10] In each case, these groups of people may subsist on diets without fresh fruits or vegetables. In addition, patients undergoing dialysis are prone to develop vitamin C deficiency,

Specific manifestation of vitamin C deficiency	*INR*	*PTT*	*Fibrinogen*	*Platelet counts (000s)*	*Evaluation of bleeding event*	*Vitamin C replacement*
Hemorrhage	1.2	36	494	337	Exploration EGD ×2	500 mg BID
Hemorrhage, hematuria	.9	24.9	475	283	Cystoscopy	250 mg q.d.
Hemorrhage, anemia	.9	29.2	529	123	Colonoscopy	500 mg BID
Anemia, GI bleed	1.1	33.6	NA	252	EGD	500 mg q.d.
Surgical bleeding, ataxia, anemia	1.1	32	288	125	EGD	250 mg q.d.
GI bleed	1.0	21.3	420	95	EGD, RBC scan	250 mg q.d.
Postop coagulopathy	1.1	25.5	249	122	Exploration	500 mg q.d.
Postop coagulopathy	1.0	27.3	165	209	Exploration	500 mg q.d.
Persistent anemia	.9	17.4	NA	409	UGI	500 mg q.d.
Postop coagulopathy	1.1	30.7	436	124	Exploration	500 mg q.d.
GI bleed	1.2	30.5	293	255	EGD, RBC scan	500 mg BID
GI bleed	.9	24.6	NA	134	EGD ×3, colonoscopy ×3	500 mg q.d.

because vitamin C is a dialyzable serum component.[9] Many people exist with borderline ascorbic acid body stores and can rapidly become deficient in the hospital after days of poor or absent oral intake. Furthermore, the onset of vitamin C deficiency is accelerated by serious illnesses such as acute pancreatitis, adult respiratory distress syndrome, and multiple organ failure.[6] These patients can quickly manifest signs of vitamin C deficiency, such as poor wound healing and hemorrhage.

Hemorrhage in patients with vitamin C deficiency is caused by a defect in vascular integrity related to the improper formation of collagen. Capillary fragility from poorly formed or easily degraded connective tissue in and around blood vessels has been described. No histologic abnormality or defect in blood clotting mechanisms has been identified in patients with vitamin C deficiency or depletion.[1,2] Normal platelet numbers and function have been demonstrated.[9] The hemorrhage associated with vitamin C deficiency has been included with other vessel-mediated bleeding disorders such as Osler-Weber-Rendu disease, Ehler-Danlos syndrome, and senile purpura.[9] Capillary fragility with vitamin C deficiency can cause chronic occult bleeding and anemia, uncontrolled spontaneous hemorrhage, or substantial surgical bleeding.[2,5,8,10-13] The typical bleeding described in patients with advanced vitamin C depletion involves massive, spontaneous hemorrhage into skin, muscles, and joints, and may be fatal if it leads to hypovolemia, coronary ischemia, or stroke.[1,4,5]

Our experience has demonstrated that vitamin C replacement can quickly reverse deficiency-related problems including hemorrhage. Others have reported the rapid cessation of diffuse hemorrhaging when vitamin C is given in doses adequate to reverse deficiency.[2,4] Within 24 hours of the first replacement dose, effective collagen cross-linking occurs and capillary stability is established. This can lead to cessation of bleeding within 24 hours. Additional manifestations of vitamin C depletion, including skin changes, can be completely reversed with 2 to 3 weeks of adequate replacement therapy.[11] A single replacement regimen for vitamin C deficiency has not been published in the literature. Absorption of vitamin C from the gastrointestinal tract involves an active transport system. This system has a transport maximum and can be saturated.[1,3] Such a transport system allows for greater bioavailability of vitamin C given in smaller, more frequent doses (250-500 mg twice a day), rather than larger doses given daily. We recommend a replacement regimen of 250 to 500 mg by mouth or nasogastric tube 2 times a day while the patient is in the hospital. Smaller doses are not sufficient to reverse the manifestations of vitamin C deficiency and will not effectively replace the deficit in total

body stores. This was well illustrated in 5 of our patients who were receiving total parenteral nutrition including daily multivitamin infusions at the time of the bleeding event. Ascorbic acid levels were low in all 5 patients. This is understandable, because the amount of vitamin C contained in a single dose of multivitamin infusion is only 125 mg. Furthermore, amounts of vitamin C included in enteral preparations vary from only 60 mg/L to 345 mg/L, and most oral multivitamins contain only 60 mg to 200 mg of vitamin C. We continue a dose of 250 to 500 mg twice daily for 1 month after discharge or longer, if dietary intake cannot maintain adequate amounts of vitamin C. Patients undergoing dialysis should receive replacement after a dialysis run. Surgical patients at high risk for vitamin C deficiency should be started on replacement therapy before elective admissions if possible. Replacement therapy may be beneficial in patients with gastrointestinal hemorrhage requiring multiple blood transfusions, those in the intensive care unit, smokers, and patients admitted for alcohol detoxification. Vitamin C deficiency may also be a marker for other nutritional deficits, which should be investigated and corrected.

We have identified 12 patients with diffuse hemorrhage, normal coagulation profiles, and low plasma ascorbic acid levels. In each patient, clinical evidence of bleeding ceased after vitamin C administration. Although this small, seminal series implies that vitamin C deficiency contributed to the bleeding diatheses in these patients, we must acknowledge the potential weaknesses of this study. Selection of a consecutive group of patients with strict entry criteria for ascorbic acid testing did not allow us to determine the incidence of vitamin C deficiency in all surgical patients or in that subset of patients with diffuse hemorrhage with abnormal coagulation parameters. No controls were designated in our analysis to better define vitamin C deficiency as the cause of bleeding or the therapeutic effect of vitamin C replacement. Finally, our review was largely retrospective. Further investigation of this fascinating relationship between vitamin C deficiency and "nonsurgical" bleeding must include ascorbic acid testing in broader groups of surgical patients, case control study designs, and basic science projects to better understand the role of vitamin C in collagen metabolism.

CONCLUSION

Although vitamin C depletion with a clinical picture of scurvy is rare, vitamin C deficiency is an under-appreciated clinical entity. A significant number of people have dietary or medical factors that place them at risk for vitamin C deficiency. Others may live with low normal vitamin C stores, and hospitalization and severe illness can quickly render them deficient in vitamin C. We have identified 12 such patients, in whom vitamin C deficiency contributed to hemorrhagic events that were quickly reversed with vitamin C replacement. The majority of patients with postoperative hemorrhage have surgical bleeding or coagulopathy from correctable causes such as hypothermia, acidosis, platelet dysfunction, thrombocytopenia, or coagulation factor depletion. However, when diffuse hemorrhage continues with no identifiable cause, and coagulation profiles are normal, vitamin C deficiency should be considered a possible origin.

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