

Short Communications

Prevalence of ascorbic acid deficiency in surgical patients and its implications for wound healing

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In January 2013 a 59-year-old man underwent an exploratory laprotomy for abdominal pain caused by diverticulitis, for which he received an appendectomy and sigmoid colectomy. Postoperatively, he suffered twice from an abdominal wound dehiscence. A remarkable recovery from a large and indolent abdominal wound was observed after supplementation with ascorbic acid (AA, 1000 mg dd orally) after a long period of insufficient wound healing (figure 1).

Case report 1

A 79-year-old woman was admitted with severe leg ulcers in 2012. She underwent a surgical intervention to remove necrotic tissue and her wounds were treated by means of pinch grafting. Post-operatively her wounds were dressed with Aquacel® Ag and changed when necessary. The wounds remained ulcerative and showed no significant healing. After 9 months of optimal wound care (Fluocinonide, Aquacel® Ag, foam dressing and Cutimed® Sorbact®) with disappointing healing, we measured her vitamin status: 25-OH vitamin D (100 nmol/L), total B12 (240 pmol/L) en folate (10.5 nmol/L) levels were normal, but her AA level was extremely low (8 umol/L, ref. 25-85 umol/L). Additionally a slight normocytic anemia was found. The patient was treated with AA supplementation (1000 mg dd orally) and starting from week 3 the patient noticed a significant improvement. After 8 weeks her ulcers were completely healed and supplementation was discontinued.

Case report 2

A second case involves a 68-year old woman, with an extensive medical history, including Crohn's disease. She had undergone an ileocecal resection correcting a perforation of the terminal ileum and as a result developed a severe case of peritonitis. Her post-surgical AA level was 4 umol/L; other vitamins measured were active vitamin B12 75 pmol/L (ref. >21 pmol/L), B1 179 nmol/L (ref. 88-157 nmol/L), B6 83 nmol/L (ref. 35-110 nmol/L), and 25-OH vitamin D 27 nmol/L (ref. 50-132 nmol/L). Due to her Crohn's disease she had a

decreased albumin level (23 g/L, ref. 29-46 g/L), and a history of anemia of the chronic disease. After 2 months another emergency laparotomy was needed because of an anastomotic leakage. Surprisingly, the abdominal fascia hardly showed any closure at all (normally the abdominal fascia should be closed after two weeks). She also suffered from multiple perforations of the transverse colon. Shortly after this laparotomy, she received 2x 500 mg dd AA intravenously (two weeks) and 2x 500 mg dd AA orally (two weeks) after which no further surgery was needed.

Case report 3

The final patient is a 56-year old man who was diagnosed with thromboangiitis obliterans (Buerger's disease) as a result of nicotine abuse. He suffered from a deep, and indolent, ulcerative wound on the lateral surface of his right ankle (Fontaine stage IV). The wound was ischemic due to the arterial insufficiency, and was intensely painful. Furthermore, a positive bacterial wound culture was found. Unfortunately, no revascularization surgery was possible, because of far advanced vascular damage. The patient was told

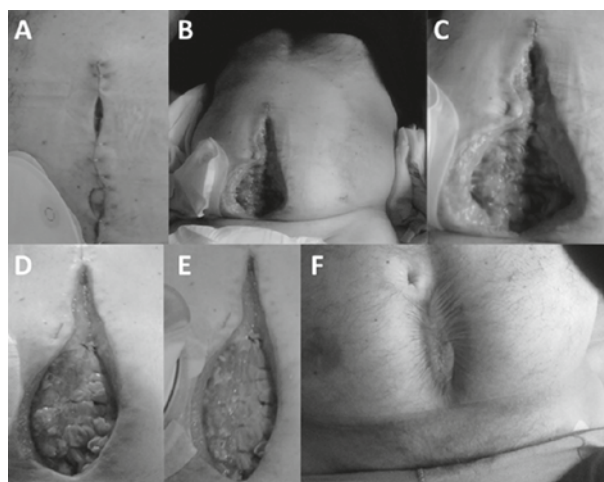


Figure 1. The abdominal wound dehiscence was surgically corrected (A). Unfortunately, the healing proces showed no progression despite optimal wound care with alginate dressings (B, C). After 6 weeks the patient was told to take ascorbic acid (AA) supplementation of 1000 mg dd orally. No changes were made in wound dressing regime. Healthy granulation tissue was seen 2,5 weeks afterwards, and woundsize was reduced to one third of its original size (D, E). 2,5 months after start of AA supplementation the wound was fully closed (F).

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to quit smoking and was started on 0,1 mg/ml iloprost (prostacyclin analogue) intravenous therapy for 3 weeks in order to improve wound healing by relieving ischemic symptoms. In the first week of treatment his laboratory results showed a low AA level of 19 umol/L. Vitamin B12 level (202 pmol/L), folic acid level (8,4 nmol/L), 25-OH vitamin D level (90 nmol/L), other laboratory parameters (hemoglobin, platelets, creatinine, CRP) were normal. This prompted us to start AA supplementation as well (500 mg, 2 dd). In one study comparing intravenous iloprost (1 ng/kg/min for 28 days) vs. placebo treatment in Buerger's disease patients a complete healing rate of 62% vs. 41% respectively was observed at week 4 and of 85% vs. 52% respectively at week 24 (1). Our patient showed a full recovery after 3 weeks from a very deep and infected ulcer with a combination therapy of iloprost and AA.

Are we blind for ascorbic acid deficiency nowadays?

Classically, major complications deriving from AA deficiency are seen in scurvy patients, however patients nowadays often do not display these hallmark characteristics. Individuals suffering from vascular disease, elderly people, pregnant women, smokers and substance abusers, malnourished people are especially prone to AA deficiency.

In our population of surgical patients (n=180) we measured AA levels (HPLC using UV detection (Recipe kit)), because they displayed poor wound healing, despite adequate wound care. In 65 out of 180 patients (36%) AA levels were below the reference limit of 25 umol/L, demonstrating a significant prevalence of AA deficiency in our pilot hospital population.

AA plays a pivotal role in collagen synthesis, where it catalyzes the conversion of procollagen to collagen (2). Because of its reducing actions it can serve as a cofactor in hydroxylation reactions, as enzyme complement, co-substrate and anti-oxidant. Dermal wound healing mainly consists of three stages, i.e. connective tissue matrix deposition, contraction and epithelialization. This is preceded by a phase of hemostasis and inflammatory activation. During tissue matrix deposition, collagen, proteoglycans and attachment proteins are deposited to create a new extracellular matrix. So-called myofibroblasts are responsible for contraction and are dependent on AA for the production collagen (3). Epithelialization in turn also depends on AA, as this high metabolic process requires increasing amounts of nutrients and oxygen. HIF-1 α is therefore upregulated by vascular

endothelial cells to increase angiogenesis by regulating vascular endothelial cell growth factor (VEGF) (4). The healing process comprises an intensive interplay of fibroblasts, epithelial cells, cytokines, and immune cells. Neutrophils and specialized macrophages play an important role in removing bacteria and tissue debris. In order to do so, they need to phagocytize and break-down these harmful pathogens for which it is believed they need AA (5). In fact, circulating white blood cells contain 10-30 times the plasma concentration of AA (6). Add the effect on inhibition of reactive oxygen species (ROS) formation in tissue cells, it is easy to see how AA deficiency could lead to ineffective wound healing (7).

Conclusion

As demonstrated in this study, AA deficiency is not uncommon in the surgical patient population. Treating deficient patients with AA leads to swift improvement of the wound healing process, thereby reducing costs of wound care and hospital stay. Further research is needed on the general prevalence of AA deficiency in surgical patients and the efficacy of supplementation on the healing process of wounds.

References

1. Bozkurt AK, Koksall C, Demirbas MY, et al. A randomized trial of intravenous iloprost (a stable prostacyclin analogue) versus lumbar sympathectomy in the management of Buerger's disease. *Int Angiol.* 2006; 25: 162-168.
2. Peterkofsky B. Ascorbate requirement for hydroxylation and secretion of procollagen: relationship to inhibition of collagen synthesis in scurvy. *Am J Clin Nutr.* 1991;54: 1135S-11340S.
3. Clark RA. Regulation of fibroplasia in cutaneous wound repair. *Am J Med Sci.* 1993; 306: 42-48.
4. Gerber HP, Condorelli F, Park J, Ferrara N. Differential transcriptional regulation of the two vascular endothelial growth factor receptor genes. Flt-1, but not Flk-1/KDR, is up-regulated by hypoxia. *J Biol Chem.* 1997; 272: 23659-23667.
5. Preedy KF, Schofield PG, Liu S, et al. Modelling contact spread of infection in host-parasitoid systems: vertical transmission of pathogens can cause chaos. *J Theor Biol.* 2010; 262: 441-451.
6. Omaye ST, Schaus EE, Kutnink MA, Hawkes WC. Measurement of vitamin C in blood components by high-performance liquid chromatography. Implication in assessing vitamin C status. *Ann N Y Acad Sci.* 1987; 498: 389-401.
7. Diegelmann RF, Evans MC. Wound healing: an overview of acute, fibrotic and delayed healing. *Front Biosci.* 2004; 9: 283-289.