The Value of High-Dose Intravenous Vitamin C

By Maureen Williams, ND

The historical use of high-dose intravenous (IV) vitamin C therapy goes back to at least the 1940s.[1] Plasma vitamin C levels can rise as much as 140- to 200-fold higher with IV treatment than with maximum tolerated oral doses (approximately 20 mM, compared to 0.1 mM), suggesting this route of administration may have a different set of therapeutic effects and a broader array of clinical indications.[2,3] A 2010 report indicated the main reasons for IV vitamin C use in clinical practice were infectious illnesses, cancer, fatigue, fibromyalgia, detoxification, and atherosclerosis.[1]

Although scurvy is uncommon in the general population, vitamin C deficiency occurs frequently in critically ill patients, as well as smokers, post-surgical and hospitalized patients, and those with chronic disease and major depression.[4] In many cases, this deficiency may be difficult to overcome with oral supplementation. IV doses of 2-3 grams per day of vitamin C can normalize circulating levels and may interrupt the cycle of tissue damage and dysfunction and rising oxidative stress levels. Higher doses, such as 6–16 grams per day have been suggested for cases of trauma, ischemia/reperfusion injury, and sepsis, since antioxidant depletion may contribute to widespread tissue damage and organ failure. IV vitamin C therapy in these cases may stimulate recovery of organ function and possibly prolong life.[5]

Safety

Although IV vitamin C is contraindicated in patients with renal failure, glucose-6-dehydrogenase deficiency, or iron or copper storage diseases, its general safety has been well demonstrated.[6] Findings from a pilot trial in six healthy men suggest concerns about increased pro-oxidant effects from vitamin C therapy may be unfounded: neither 750 nor 7,500 mg of IV vitamin C per day for six consecutive days raised markers of oxidative stress.[7] In fact, a meta-analysis of 12 studies including a combined total of 446 participants showed that vitamin C therapy lowered levels of C-reactive protein (CRP), an inflammatory marker associated with oxidative stress. The effect was strongest in those under 60 years of age, those with higher baseline CRP levels, and those receiving their vitamin C intravenously.[8]

A small amount (less than 0.5%) of large doses of vitamin C is converted to oxalate,[9] but reports of renal stones possibly related to IV vitamin C are rare and limited to patients with renal dysfunction.[6,10]

It is important to note IV vitamin C administration can falsely elevate blood glucose readings on some self-monitoring devices, which may lead to excessive insulin use and hypoglycemia.[11,12]

Anecdotal Evidence

The potential benefits of IV vitamin C were documented as early as the 1940s by Dr. Frederick Robert Klenner, who reported numerous successful cases using large doses of sodium

ascorbate intravenously to treat viral pneumonia, measles, chicken pox, polio, and other viral infections.[13-16] In a paper published in the Journal of Applied Nutrition in 1971, Klenner summarized his observations and experiences using high-dose ascorbic acid.[17] In the paper, Klenner described his methods for determining vitamin C status and requirements of individuals, and proposed the Silver Nitrate-Urine Test as the most useful for ascertaining the oral, intramuscular, or IV dosage needed. He went on to detail his theories regarding the antiviral actions of vitamin C, and presented a case in which a patient hospitalized with unconsciousness and high fever attributed to viral pneumonia was treated successfully with 140 grams of ascorbic acid, administered over 72 hours. Finally, he described the potential benefits of high-dose vitamin C therapy in patients with third-degree burns, recurring miscarriage, insect and snake bites, poisonings, tetanus, and viral hepatitis, as well as post-surgical patients in general. He recommended IV doses ranging from 350–1,200 mg per kg body weight, and provided instructions on preparing the IV solution.

In the 1980s, Dr. Robert F Cathcart, III, published a series of articles detailing his experience and recommendations regarding high-dose ascorbate therapy. Cathcart introduced the concept of bowel tolerance as a method for determining oral vitamin C dose, and reported that bowel tolerance can increase from approximately 4–15 grams per 24 hours in health to as much as 200 grams per 24 hours at the peak of an acute illness due to a phenomenon he called “acute induced scurvy”. Furthermore, he suggested the degree of vitamin C tolerance increases with severity of illness.[18] He noted this same relationship is seen in allergy patients, who may tolerate oral doses as high as 50 grams per day during periods of high antigenic exposure.[19] Cathcart suggested large amounts of vitamin C are needed to scavenge free radicals produced at high rates during tissue inflammation,[20] and provided his recommendations for high-dose ascorbate therapy, administered intravenously when necessary, in cases of bacterial, viral, and fungal infections; to treat allergies; in post-surgery or trauma patients; for autoimmune rheumatic conditions; and, in cancer patients.[21] He proposed sudden infant death syndrome is caused by acute induced scurvy and might be preventable with high-dose ascorbate treatment[18,22] and, prior to the availability of effective antiviral medication protocols, he was a proponent of high-dose ascorbate therapy in patients with HIV/AIDs to affect the course of the viral infection and prevent secondary infections.[23]

Dr. Thomas E. Levy is a more contemporary supporter of high-dose vitamin C therapy. In his writing, he described his rationale for recommending sodium or magnesium ascorbate for high dose administration: low cost, safety, and, in the case of magnesium ascorbate, potential additional benefits from the cationic portion of the ascorbate salt.[24] Levy also described a method for achieving maximum blood ascorbate concentrations using pulsed IV sodium ascorbate. His protocol includes 20-gram vitamin C pushes over 2 minutes, while cautioning that this can cause a rapid release of pancreatic insulin leading to hypoglycemia.[25] In another paper, Levy reports on a case of flu treated with 50 grams of sodium ascorbate administered intravenously along with small amounts of calcium gluconate, magnesium sulfate, and B complex vitamins (without B12), as well as 6 grams of glutathione added at the end of the infusion. This was followed by dramatic improvement, which continued with five subsequent

daily repetitions of this treatment, though with the calcium removed and dose of sodium ascorbate increased to 100 grams.[26]

Effects of Vitamin C on Cortisol and Insulin

A 1993 report from a research team looking at the effects of high-dose vitamin C in a healthy individual noted: IV infusion was more effective than IV injection for sustaining high blood vitamin C concentrations; and, vitamin C infusion triggered an increase in insulin output. The team also reported that, in three patients with diabetes, vitamin C infusions in conjunction with insulin injections led to clinical improvement.[27] The same research team conducted other experiments in healthy individuals, in which they demonstrated IV vitamin C infusion triggered a surge in ACTH and cortisol levels, followed by rapid cortisol depletion.[28,29] The implications of these findings await further investigation.

Clinical Evidence

Blood Vessel Function

Vitamin C has demonstrated positive effects on vascular health and function in numerous studies. Interestingly, oxygen therapy, a standard intervention in patients with shortness of breath widely used in emergency medicine, can elevate free radical production and critically stiffen coronary blood vessels and reduce cardiac output. A pilot trial in eight healthy men found these effects were eliminated by a 3-gram IV infusion of vitamin C administered over 15 minutes before treatment with 100% oxygen.[30]

One trial noted IV vitamin C at doses higher than 30 grams acutely lowered blood pressure in pre-hypertensive individuals being treated for other conditions: systolic blood pressure decreased an average of 8–9 mmHg and diastolic blood pressure decreased 6–7 mmHg during IV therapy.[31] In healthy sedentary postmenopausal women, carotid artery flexibility was diminished compared to premenopausal women, but normal carotid artery responsiveness was restored with IV vitamin C therapy.[32]

High blood pressure and high cholesterol levels are associated with coronary artery dysfunction and increased risk of atherosclerosis. In a controlled trial, 3 grams of IV vitamin C reduced experimental coronary vasoconstriction in subjects with high blood pressure or high cholesterol levels and restored coronary function similar to that seen in healthy subjects.[33] Obstructive sleep apnea is also associated with poor vascular function. In a trial in otherwise healthy people with obstructive sleep apnea, a 0.5 gram infusion of vitamin C improved endothelial function to levels seen in healthy individuals without sleep apnea.[34] Hyperglycemia can also compromise blood vessel function, and IV ascorbate, at a dose of 2 grams, has been shown to prevent the change in vascular function and rise in blood pressure induced by acute hyperglycemia in healthy men.[35,36] In addition, in a group of 20 study participants with type I diabetes subjected to experimental hypoglycemia, IV vitamin C (30 mg per minute for two hours) reduced endothelial oxidative stress, inflammation, and dysfunction.[37]

In a placebo-controlled crossover trial in 10 heart failure patients, 2 grams of IV vitamin C was found to improve endothelial function and increase the antiplatelet effect of certain vasodilating compounds.[38] In patients undergoing coronary artery stent, IV vitamin C (1 gram over approximately 40 minutes) prior to the procedure reduced a post-stent rise in platelet activation and production of a pro-inflammatory and pro-coagulant molecule.[39]

Cancer

The first reports suggesting IV vitamin C therapy reduces mortality in cancer patients was published in 1976 by Drs. Linus Pauling and Ewan Cameron.[40] Subsequent trials using high doses of oral vitamin C yielded disappointing results, indicating the importance of achieving pharmacologic plasma levels in obtaining positive results. Since then, researchers have sought to understand the mechanisms and limitations of IV vitamin C therapy in cancer treatment. The prevailing theory is that ascorbate increases intracellular oxidative stress via generation of hydrogen peroxide, an effect that is selectively toxic to cancer cells, possibly due to increased levels of reactive iron and other metal ions in cancer cells.[3] Another possible mechanism involves disruption of glucose metabolism.[41] Laboratory research indicates pharmacologic concentrations of vitamin C increase cancer cell susceptibility to chemotherapy agents and radiation therapy. Indeed, this sensitizing effect has been noted in studies using cancer cell lines including small cell lung, ovarian, gastric, colon, brain, blood, and connective tissue cancers. [3,41] Furthermore, vitamin C, even at high concentrations, acts as a protective antioxidant in metabolically normal tissues, and may improve tolerance of standard anticancer therapies.[3]

More recent clinical studies have evaluated IV vitamin C therapy alone and in conjunction with standard anticancer treatments. The only randomized controlled trial to date compared standard chemotherapy to chemotherapy plus IV vitamin C (75 or 100 mg twice weekly for 12 months) in stage III/IV ovarian cancer. Those receiving IV vitamin C had fewer treatment-related toxicities and lengthened progression-free survival.[42] Although results from other studies have been mixed, there is no evidence that IV vitamin C interferes with conventional approaches.[42,43] In addition, a growing body of research suggests IV vitamin C may reduce off-target toxicity and improve quality of life in cancer patients undergoing cancer treatment.[6,44,45]

Sepsis

Vitamin C has shown promise as a treatment for sepsis, a severe infectious condition marked by overwhelming free radical production, vascular dysfunction, cellular and mitochondrial injury, and progressive organ failure.[46,47] The addition of thiamin (vitamin B1) may enhance the effects of vitamin C by supporting cellular metabolism and energy production. In one study, mortality rates were similar in the 229 sepsis patients who received 3 grams per 12 hours of vitamin C plus 200 mg per 12 hours of thiamin within six hours of onset of septic shock and 915 sepsis patients who did not receive vitamin therapy; however, IV vitamin C plus thiamin therapy was associated with lower in-hospital mortality in a subgroup of those with the worst prognosis.[48]

A meta-analysis that included five studies with a combined total of 142 hospitalized patients in critical states found promising effects of high-dose IV vitamin C therapy on the length of time mechanical ventilation and medical interventions to normalize vascular function were required;

however, no effect on mortality was noted.[49] Another meta-analysis noted a small but statistically non-significant benefit on mortality for IV vitamin C in critically ill patients.[50] More research is needed to elucidate the potential benefits of this IV vitamin C treatment in critically ill hospitalized patients.

Neuralgia and Neuropathy

IV vitamin C therapy has been reported to relieve nerve pain due to various causes. For example, the IV administration of 3 grams of vitamin C during the first 30 minutes of surgery reduced post-surgical pain more effectively than placebo in a study in adults undergoing throat surgery and tonsillectomy.[51] Another study included 100 participants scheduled for laparoscopic colon surgery. They received vitamin C, at doses of 50 mg per kilogram body weight, or placebo intravenously during the first 30 minutes of surgery. Those who received vitamin C had lower pain scores and used less morphine during the 24 hours after surgery.[52] In a case report, IV vitamin C therapy helped to relieve nerve pain caused by extensive jellyfish stings.[53] IV vitamin C may even be helpful in patients with a nerve disorder known as idiopathic sudden sensorineural hearing loss, or sudden deafness: 36 patients treated with high-dose IV vitamin C therapy (200 mg per kilogram body weight) for 10 days along with standard corticosteroid therapy, followed by oral vitamin C (2,000 mg per day) for 30 days, were more likely to experience partial or complete restoration of hearing compared to 36 patients treated with standard therapy alone.[54]

Herpes zoster (shingles) is caused by reactivation of a dormant herpes virus and manifests as a blistering skin rash and nerve pain that is notoriously severe. Post-herpetic neuralgia is a physically and mentally debilitating complication in which nerve pain persists for three to six months or, in rare cases, even longer. Post-herpetic neuralgia risk has been correlated with lower blood vitamin C levels.[55] Studies suggest IV vitamin C therapy may have a role in treatment of acute herpes zoster pain and prevention of post-herpetic neuralgia. In a placebo-controlled trial that included 87 patients with herpes zoster, participants received either 5 grams of IV ascorbate or placebo on days 1, 3, and 5 of the study, and were monitored for 16 weeks. Although vitamin C did not relieve acute herpes zoster pain, it did reduce the incidence of post-herpetic neuralgia.[56] In an uncontrolled pilot trial with 67 participants suffering from herpes zoster, treatment with 7.5 grams of IV vitamin C two to four times per week for approximately two weeks appeared to reduce pain, fatigue, and poor concentration, as well as risk of post-herpetic neuralgia.[57] In a case report of a woman with herpes zoster neuralgia lasting 10 days that was unresponsive to other therapies, IV vitamin C treatment (4 grams daily for five days) resulted in quick and full resolution of pain, allowing her to discontinue opioid and other analgesics.[58] Other reports describe cases of acute herpetic pain resolving after treatment with 15 grams of IV vitamin C administered every second day for about two weeks.[59]

Viral Infections

Although pioneers of IV vitamin C therapy used it to treat viral infections, few clinical trials have examined its effects. One study examined data from 178 cases of Epstein-Barr virus (EBV) infection, manifesting mainly as mononucleosis or chronic fatigue syndrome, treated at a single facility over nine years. Five or more treatments with 15–30 grams of IV vitamin C was

associated with reductions in EBV antibody levels and shortened duration of illness.[60] In a case report, an impressive recovery from acute respiratory distress syndrome caused by viral infection in a 20-year old female was described: After three days with poor response to conventional treatments and in the face of rapidly progressing respiratory dysfunction, treatment with high-dose IV vitamin C (200 mg per kilogram body weight, divided into four daily doses six hours apart) was initiated. This was followed by rapid improvement and eventual recovery.[60]

Allergies

In a trial that included 19 patients with allergies and 70 patients with infectious illnesses, IV infusion of 7.5 grams of vitamin C was found to reduce histamine levels, and the effect was greater in those with higher baseline histamine levels and those with allergies in general.[61] A larger uncontrolled trial examined the effects of IV vitamin C therapy in 71 participants with acute or chronic allergic conditions. Treatment with 7.5 grams of IV vitamin C two to three times per week for an average of 3 weeks in those with acute allergies and 12 weeks in those with chronic allergies led to significant reductions in allergy-specific symptoms such as pruritis, rhinitis, and restlessness, as well as non-specific symptoms such as fatigue, sleep difficulties, depression, and poor concentration.[62]

Functional Iron Deficiency

Functional iron deficiency, characterized by high serum ferritin and low transferrin saturation, is common in people who require regular hemodialysis for chronic kidney disease. Because vitamin C can mobilize stored iron,[63] the effect of IV vitamin C therapy on iron status in this population has been the subject of several studies. A pilot trial showed that 500 mg of IV vitamin C administered over 30 minutes at the end of hemodialysis twice weekly effectively improved iron status in 20 of 33 treated patients.[64] In another trial, treatment with 300 mg of IV ascorbate three times weekly for eight weeks resolved functional iron deficiency in 18 of 37 participants.[65] The same dose twice weekly for five weeks was found to be as effective at reversing functional iron deficiency as 100 mg of IV iron sucrose twice weekly for five weeks in a comparison trial.[66]

Fatigue

A trial with 141 healthy volunteers compared the effects of an IV treatment with 10 grams of vitamin C to placebo. Those receiving vitamin C had reported lower levels of fatigue two hours after treatment and again one day later. The effect was more pronounced in those with lower baseline vitamin C levels.[67]

Acute Pancreatitis

One study that included 84 participants with acute pancreatitis reported benefits associated with high-dose IV vitamin C therapy. The study's participants received either 10 grams of IV vitamin C or 1 gram of IV vitamin C per day for five days. Those treated with the higher dose experienced faster and more complete recovery, fewer complications, and shorter hospital stays compared with those receiving the lower dose.[68]

References:

1. Padayatty SJ, Sun AY, Chen Q, Espey MG, Drisko J, Levine M. Vitamin C: intravenous use by complementary and alternative medicine practitioners and adverse effects. *PloS one.* 2010;5(7):e11414.
2. Padayatty SJ, Sun H, Wang Y, et al. Vitamin C pharmacokinetics: implications for oral and intravenous use. *Annals of internal medicine.* 2004;140(7):533-537.
3. Schoenfeld JD, Alexander MS, Waldron TJ, et al. Pharmacological Ascorbate as a Means of Sensitizing Cancer Cells to Radio-Chemotherapy While Protecting Normal Tissue. *Seminars in radiation oncology.* 2019;29(1):25-32.
4. Klimant E, Wright H, Rubin D, Seely D, Markman M. Intravenous vitamin C in the supportive care of cancer patients: a review and rational approach. *Current oncology (Toronto, Ont).* 2018;25(2):139-148.
5. Spoelstra-de Man AME, Elbers PWG, Oudemans-Van Straaten HM. Vitamin C: should we supplement? *Current opinion in critical care.* 2018;24(4):248-255.
6. Carr AC, Cook J. Intravenous Vitamin C for Cancer Therapy - Identifying the Current Gaps in Our Knowledge. *Frontiers in physiology.* 2018;9:1182.
7. Muhlhofer A, Mrosek S, Schlegel B, et al. High-dose intravenous vitamin C is not associated with an increase of pro-oxidative biomarkers. *European journal of clinical nutrition.* 2004;58(8):1151-1158.
8. Jafarnejad S, Boccardi V, Hosseini B, Taghizadeh M, Hamedifard Z. A Meta-analysis of Randomized Control Trials: The Impact of Vitamin C Supplementation on Serum CRP and Serum hs-CRP Concentrations. *Current pharmaceutical design.* 2018;24(30):3520-3528.
9. Robitaille L, Mamer OA, Miller WH, Jr., et al. Oxalic acid excretion after intravenous ascorbic acid administration. *Metabolism: clinical and experimental.* 2009;58(2):263-269.
10. Prier M, Carr AC, Baillie N. No Reported Renal Stones with Intravenous Vitamin C Administration: A Prospective Case Series Study. *Antioxidants (Basel, Switzerland).* 2018;7(5).
11. Vasudevan S, Hirsch IB. Interference of intravenous vitamin C with blood glucose testing. *Diabetes care.* 2014;37(5):e93-94.
12. Sharma E, Resta C, Park P. A Case of Factitious Hyperglycemia in a Patient on Intravenous Ascorbic Acid. *Case reports in endocrinology.* 2018;2018:7063137.
13. Klenner FR. Virus pneumonia and its treatment with vitamin C. *Southern medicine and surgery.* 1948;110(2):36-38.
14. Klenner FR. The treatment of poliomyelitis and other virus diseases with vitamin C. *Southern medicine and surgery.* 1949;111(7):209-214.
15. Klenner FR. Massive doses of vitamin C and the virus diseases. *Southern medicine and surgery.* 1951;113(4):101-107.
16. Klenner FR. The vitamin and massage treatment for acute poliomyelitis. *Southern medicine and surgery.* 1952;114(8):194-197.
17. Klenner FR. Observations On the Dose and Administration of Ascorbic Acid When Employed Beyond the Range Of A Vitamin In Human Pathology. *Journal of Applied Nutrition.* 1971;23(3&4).

18. Cathcart RF, 3rd. Vitamin C: the nontoxic, nonrate-limited, antioxidant free radical scavenger. *Medical hypotheses.* 1985;18(1):61-77.
19. Cathcart RF, 3rd. The vitamin C treatment of allergy and the normally unprimed state of antibodies. *Medical hypotheses.* 1986;21(3):307-321.
20. Cathcart RF. A unique function for ascorbate. *Medical hypotheses.* 1991;35(1):32-37.
21. Cathcart RF. The method of determining proper doses of vitamin C for the treatment of diseases by titrating to bowel intolerance. *The Australasian nurses journal.* 1980;9(4):9-13.
22. Cathcart RF. Vitamin C, titrating to bowel tolerance, anascorbemia, and acute induced scurvy. *Medical hypotheses.* 1981;7(11):1359-1376.
23. Cathcart RF, 3rd. Vitamin C in the treatment of acquired immune deficiency syndrome (AIDS). *Medical hypotheses.* 1984;14(4):423-433.
24. Levy TE. The Many Faces of Vitamin C. *Health E-Bytes.* 2005(9).
25. Levy TE. Pulsed intravenous vitamin C (PIVC) therapy. *Health E-Bytes.* 2003(6).
26. Levy TE. Vitamin C and severe influenza: A case report. *Health E-Bytes.* 2003(7).
27. Kodama M, Kodama T, Murakami M, Kodama M. Diabetes mellitus is controlled by vitamin C treatment. *In vivo (Athens, Greece).* 1993;7(6a):535-542.
28. Kodama M, Kodama T, Murakami M, Kodama M. Vitamin C infusion treatment enhances cortisol production of the adrenal via the pituitary ACTH route. *In vivo (Athens, Greece).* 1994;8(6):1079-1085.
29. Kodama M, Kodama T, Murakami M, Kodama M. Autoimmune disease and allergy are controlled by vitamin C treatment. *In vivo (Athens, Greece).* 1994;8(2):251-257.
30. Gao Z, Spilk S, Momen A, Muller MD, Leuenberger UA, Sinoway LI. Vitamin C prevents hyperoxia-mediated coronary vasoconstriction and impairment of myocardial function in healthy subjects. *European journal of applied physiology.* 2012;112(2):483-492.
31. Ried K, Travica N, Sali A. The acute effect of high-dose intravenous vitamin C and other nutrients on blood pressure: a cohort study. *Blood pressure monitoring.* 2016;21(3):160-167.
32. Moreau KL, Gavin KM, Plum AE, Seals DR. Ascorbic acid selectively improves large elastic artery compliance in postmenopausal women. *Hypertension (Dallas, Tex : 1979).* 2005;45(6):1107-1112.
33. Jeserich M, Schindler T, Olschewski M, Unmussig M, Just H, Solzbach U. Vitamin C improves endothelial function of epicardial coronary arteries in patients with hypercholesterolaemia or essential hypertension--assessed by cold pressor testing. *European heart journal.* 1999;20(22):1676-1680.
34. Grebe M, Eisele HJ, Weissmann N, et al. Antioxidant vitamin C improves endothelial function in obstructive sleep apnea. *American journal of respiratory and critical care medicine.* 2006;173(8):897-901.
35. Mullan BA, Ennis CN, Fee HJ, Young IS, McCance DR. Protective effects of ascorbic acid on arterial hemodynamics during acute hyperglycemia. *American journal of physiology Heart and circulatory physiology.* 2004;287(3):H1262-1268.
36. Mullan BA, Ennis CN, Fee HJ, Young IS, McCance DR. Pretreatment with intravenous ascorbic acid preserves endothelial function during acute hyperglycaemia (R1). *Clinical and experimental pharmacology & physiology.* 2005;32(5-6):340-345.

37. Ceriello A, Novials A, Ortega E, et al. Vitamin C further improves the protective effect of glucagon-like peptide-1 on acute hypoglycemia-induced oxidative stress, inflammation, and endothelial dysfunction in type 1 diabetes. *Diabetes care.* 2013;36(12):4104-4108.
38. Ellis GR, Anderson RA, Chirkov YY, et al. Acute effects of vitamin C on platelet responsiveness to nitric oxide donors and endothelial function in patients with chronic heart failure. *Journal of cardiovascular pharmacology.* 2001;37(5):564-570.
39. Pignatelli P, Tanzilli G, Carnevale R, et al. Ascorbic acid infusion blunts CD40L upregulation in patients undergoing coronary stent. *Cardiovascular therapeutics.* 2011;29(6):385-394.
40. Cameron E, Pauling L. Supplemental ascorbate in the supportive treatment of cancer: Prolongation of survival times in terminal human cancer. *Proceedings of the National Academy of Sciences.* 1976;73(10):3685-3689.
41. Park S, Ahn S, Shin Y, Yang Y, Yeom CH. Vitamin C in Cancer: A Metabolomics Perspective. *Frontiers in physiology.* 2018;9:762.
42. Ma Y, Chapman J, Levine M, Polireddy K, Drisko J, Chen Q. High-dose parenteral ascorbate enhanced chemosensitivity of ovarian cancer and reduced toxicity of chemotherapy. *Science translational medicine.* 2014;6(222):222ra218.
43. Nauman G, Gray JC, Parkinson R, Levine M, Paller CJ. Systematic Review of Intravenous Ascorbate in Cancer Clinical Trials. *Antioxidants (Basel, Switzerland).* 2018;7(7).
44. Bazzan AJ, Zabrecky G, Wintering N, Newberg AB, Monti DA. Retrospective Evaluation of Clinical Experience With Intravenous Ascorbic Acid in Patients With Cancer. *Integrative cancer therapies.* 2018;17(3):912-920.
45. Carr AC, Vissers MC, Cook JS. The effect of intravenous vitamin C on cancer- and chemotherapy-related fatigue and quality of life. *Frontiers in oncology.* 2014;4:283.
46. Marik PE. Vitamin C for the treatment of sepsis: The scientific rationale. *Pharmacology & therapeutics.* 2018;189:63-70.
47. Wilson JX. Mechanism of action of vitamin C in sepsis: ascorbate modulates redox signaling in endothelium. *BioFactors (Oxford, England).* 2009;35(1):5-13.
48. Shin TG, Kim YJ, Ryoo SM, et al. Early Vitamin C and Thiamine Administration to Patients with Septic Shock in Emergency Departments: Propensity Score-Based Analysis of a Before-and-After Cohort Study. *Journal of clinical medicine.* 2019;8(1).
49. Zhang M, Jativa DF. Vitamin C supplementation in the critically ill: A systematic review and meta-analysis. *SAGE open medicine.* 2018;6:2050312118807615.
50. Langlois PL, Manzanares W, Adhikari NKJ, et al. Vitamin C Administration to the Critically Ill: A Systematic Review and Meta-Analysis. *JPEN Journal of parenteral and enteral nutrition.* 2018.
51. Ayatollahi V, Dehghanpour Farashah S, Behdad S, Vaziribozorg S, Rabbani Anari M. Effect of intravenous vitamin C on postoperative pain in uvulopalatopharyngoplasty with tonsillectomy. *Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery.* 2017;42(1):139-143.
52. Jeon Y, Park JS, Moon S, Yeo J. Effect of Intravenous High Dose Vitamin C on Postoperative Pain and Morphine Use after Laparoscopic Colectomy: A Randomized Controlled Trial. *Pain research & management.* 2016;2016:9147279.

53. Kumar S, Miranda-Massari JR, Gonzalez MJ, Riordan HD. Intravenous ascorbic acid as a treatment for severe jellyfish stings. *Puerto Rico health sciences journal.* 2004;23(2):125-126.
54. Kang HS, Park JJ, Ahn SK, Hur DG, Kim HY. Effect of high dose intravenous vitamin C on idiopathic sudden sensorineural hearing loss: a prospective single-blind randomized controlled trial. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery.* 2013;270(10):2631-2636.
55. Chen JY, Chang CY, Feng PH, Chu CC, So EC, Hu ML. Plasma vitamin C is lower in postherpetic neuralgia patients and administration of vitamin C reduces spontaneous pain but not brush-evoked pain. *The Clinical journal of pain.* 2009;25(7):562-569.
56. Kim MS, Kim DJ, Na CH, Shin BS. A Study of Intravenous Administration of Vitamin C in the Treatment of Acute Herpetic Pain and Postherpetic Neuralgia. *Annals of dermatology.* 2016;28(6):677-683.
57. Schencking M, Vollbracht C, Weiss G, et al. Intravenous vitamin C in the treatment of shingles: results of a multicenter prospective cohort study. *Medical science monitor : international medical journal of experimental and clinical research.* 2012;18(4):Cr215-224.
58. Byun SH, Jeon Y. Administration of Vitamin C in a Patient with Herpes Zoster - A case report. *The Korean journal of pain.* 2011;24(2):108-111.
59. Schencking M, Sandholzer H, Frese T. Intravenous administration of vitamin C in the treatment of herpetic neuralgia: two case reports. *Medical science monitor : international medical journal of experimental and clinical research.* 2010;16(5):Cs58-61.
60. Fowler Iii AA, Kim C, Lepler L, et al. Intravenous vitamin C as adjunctive therapy for enterovirus/rhinovirus induced acute respiratory distress syndrome. *World journal of critical care medicine.* 2017;6(1):85-90.
61. Hagel AF, Layritz CM, Hagel WH, et al. Intravenous infusion of ascorbic acid decreases serum histamine concentrations in patients with allergic and non-allergic diseases. *Naunyn-Schmiedeberg's archives of pharmacology.* 2013;386(9):789-793.
62. Vollbracht C, Raithel M, Krick B, Kraft K, Hagel AF. Intravenous vitamin C in the treatment of allergies: an interim subgroup analysis of a long-term observational study. *The Journal of international medical research.* 2018;46(9):3640-3655.
63. Handelman GJ. New insight on vitamin C in patients with chronic kidney disease. *Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation.* 2011;21(1):110-112.
64. Kang DW, Ahn CY, Ryu BK, Shin BC, Chung JH, Kim HL. The effect of intravenous ascorbic acid in hemodialysis patients with normoferritinemic anemia. *Kidney research and clinical practice.* 2012;31(1):48-53.
65. Tarng DC, Wei YH, Huang TP, Kuo BI, Yang WC. Intravenous ascorbic acid as an adjuvant therapy for recombinant erythropoietin in hemodialysis patients with hyperferritinemia. *Kidney international.* 1999;55(6):2477-2486.
66. Sedighi O, Makhlough A, Janbabai G, Neemi M. Comparative study of intravenous iron versus intravenous ascorbic Acid for treatment of functional iron deficiency in patients

under hemodialysis: a randomized clinical trial. *Nephro-urology monthly.* 2013;5(4):913-917.

67. Suh SY, Bae WK, Ahn HY, Choi SE, Jung GC, Yeom CH. Intravenous vitamin C administration reduces fatigue in office workers: a double-blind randomized controlled trial. *Nutrition journal.* 2012;11:7.
68. Du WD, Yuan ZR, Sun J, et al. Therapeutic efficacy of high-dose vitamin C on acute pancreatitis and its potential mechanisms. *World journal of gastroenterology.* 2003;9(11):2565-2569.