



Review

High-dose vitamin C and cancer

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ABSTRACT

Vitamin C (ascorbic acid, ascorbate) is a basic compound that is of great importance with its role in various enzymatic reactions including the synthesis of collagen, as well as with its redox functions. Vitamin C has become the center of interest in cancer studies, in consequence of the facts that connective tissue changes and vitamin C deficiency were first alleged to be associated with cancer in the 1950s; and that high doses of vitamin C was asserted to be cytotoxic for cancer cells, later on. The results of the first study carried out in the 1970s were promising; but afterwards, the studies were ascertained to be faulty. Despite the positive results achieved from some laboratory and animal experiments, randomized clinical trials did not verify those findings, and no clear benefit of vitamin C for cancer treatment could be demonstrated. As for studies, where its use in combination with other cancer treatment regimens was assessed, conflicting results were obtained. Although intake of high doses of vitamin C is alleged to be harmless, based on that it is in the group of water soluble vitamins and is not stored in the body, there are many side effects and drug interactions reported in the literature. For now, it is better to abstain from this treatment, until the benefit of the treatment (if any) is clearly demonstrated, considering the potential side effects and interactions.

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1. Introduction

Vitamin C, also known as ascorbic acid and ascorbate, is a basic compound that belongs to the group of water-soluble vitamins. It has L- and D-enantiomer, but D-enantiomer is not available in nature and has no physiological significance; therefore, it always refers to the L-enantiomer of ascorbic acid and ascorbate, unless written otherwise.¹ Vitamin C can be produced by most animals and plants from D-glucose and D-galactose, whereas it is not produced in humans due to the lack of L-gulonolactone oxidase enzyme; and therefore, it should be taken externally.² The World Health Organization (WHO) recommends a daily intake of 45 mg C per day for healthy adults.³

The biological importance of vitamin C is that it plays a cofactor role, as a reducing agent, in various enzymatic reactions. Because it has a low redox potential of 280 mV, it has the potential to react with almost all other oxidized free radicals. Therefore, it is used as

an antioxidant. Vitamin C is also a compound that plays an important role in collagen synthesis.² Vitamin C is also responsible in the synthesis of carnitine and various neurotransmitters as well as tyrosine metabolism and microsomal metabolism.⁴ Because it is available in high concentrations in the immune cells, and is rapidly consumed in the body in case of any infection, it is thought to be associated with the immune system, as well. However, its mechanism has yet to be clearly elucidated.⁵ Severe vitamin C deficiency leads to gum recession, weakness, lethargy, and scurvy characterized by easy bleeding and bruising. The symptoms of scurvy develop as a result of weakened connective tissue in the body, and vitamin C is given to patients with scurvy for strengthening their connective tissues.⁶

Some alternative medicine proponents assert that high doses of vitamin C can be used in the treatment of cancer. But although promising results have been achieved from some laboratory and animal studies, these assertions have not been supported by clinical studies on humans. In some studies, when it has been combined with other treatment regimens, some effects have been observed but specific contribution of high-dose vitamin C to those results could not be shown.^{7–10}

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2. History of vitamin C

For the first time in 1753, citrus fruits were asserted to prevent scurvy; and upon that, the way of the path to the discovery of vitamin C was opened. In 1912, the scientist Casimir Funk coined the term “antiscorbutic vitamin” to refer this compound contained in fruits and vegetables. In 1920, the British biochemist Jack Drummond used the term “vitamin C” to refer this compound.^{11–13} For the first time in a study conducted in 1959, it was asserted that cancer could be associated with connective tissue changes, and such a condition could be associated with a deficiency in vitamin C. Upon this assertion, the use of vitamin C in cancer treatment became a topic of conversation.¹⁴ High-dose vitamin C began to be tried by the Scottish surgeon Ewan Cameron for the first time in 1970, in his studies on cancer patients. Afterward, the studies attracted greater interest upon the participation of the Nobel Prize winner Linus Pauling. As a result of their studies on patients with advanced cancer, Cameron and Pauling asserted that high-dose ascorbic acid can enhance the body resistance and can be a potential therapy agent for cancer, but those studies were then found to be faulty.^{15–19}

3. What is high dose?

The general consensus among practitioners is that high-dose intravenous vitamin C (HDIVC) is greater than 10 g/infusion and low-dose intravenous vitamin C (LDIVC) is less than 10 g/infusion.

4. Potential side effects of high-dose vitamin C

Although intake of high doses of vitamin C is alleged to be harmless, based on that it is a water soluble vitamin and is not stored in the body, there are many side effects and drug interactions reported in the literature. It has been reported that high-dose vitamin C could increase hemolytic anemia in those who have Glucose-6-phosphate dehydrogenase deficiency; and the risk of renal failure in those who have renal disorders.^{20,21} In addition, because vitamin C may increase the bioavailability of iron, its use in hemochromatosis patients is not recommended.²² Furthermore, vitamin B12 and copper absorption can be reduced, as well.²³ Because vitamin C acidifies the urine, it can cause the formation of kidney stones; and on the other hand, a case of hyperoxaluria may emerge due to oxalic acid formed as a result of vitamin C metabolism.²⁴ In a study published in 2000, the tolerable upper limit of vitamin C was determined—for the first time—to be 2 g, and amounts exceeding this limit were reported to have a laxative effect. Diarrhea is already the most common side effect of high-doses vitamin C.²⁵

In the literature, there are studies showing that the use of high-dose vitamin C in combination with certain chemotherapy drugs increases the toxicity. It has been shown that the use of high-dose vitamin C in combination with arsenic trioxide in acute myeloid leukemia, refractory metastatic colon cancer, and metastatic melanoma causes serious side effects and leads to the disease's progression.^{9,10,26} And in some studies, researchers had to discontinue their studies due to unexpected effects.^{27,28}

5. Laboratory studies on the effects of high-dose vitamin in cancer

In some laboratory studies, pharmacological doses of vitamin C (0.1–100 mM) were shown to reduce proliferation in cell lines in various types of cancer. The potential mechanism of this effect of vitamin C was investigated in laboratory studies, as well; and high-dose-vitamin C was shown to create cytotoxic effect on cancer cells,

by means of chemical reactions that produce hydrogen peroxide.^{29–32} In laboratory studies again, pharmacological doses of ascorbic acid increased the effect of arsenic trioxide in ovarian cancer cells; gemcitabine in pancreatic cancer cells; and the combination of gemcitabine and epigallocatechin-3-gallate (EGCG) in mesothelioma cells.^{33–35} In a study conducted in 2012, high-dose ascorbate was reported to increase the radiosensitivity of glioblastoma multiforme cells.³⁶ But in some studies, it was reported to reduce the effect of the drug, when used in combination with certain chemotherapy drugs such as doxorubicin, methotrexate, and cisplatin.³⁷

6. Clinical studies on the effects of high-dose vitamin in cancer

The first clinical studies on the effects of high-dose vitamin C were carried out in the 1970s, by Linus Pauling and Ewan Cameron. Dr. Cameron and the chemist Pauling asserted, as a result of their studies, that IV (intravenous) administration of high-dose vitamin C significantly prolongs the survival of advanced-stage cancer patients.^{15,16,19} However, when their studies were evaluated by the National Cancer Institute later on, they were concluded to be poorly designed and inaccurate. In addition, any of the 3 studies conducted by the Mayo Clinic did not prove the results.^{17,18}

In two randomized controlled trials, where the effect of orally administered high-dose vitamin C was evaluated, the patients were divided into 2 groups, who were then assigned to treatment with either high-dose vitamin C (10 g daily) or placebo. At the end of the study, no significant difference was observed between the groups, in terms of survival and quality of life.^{38,39} In pharmacokinetic studies performed later on, the maximum concentration of vitamin C that could be reached in the blood varied depending on the way of administration of the treatment. When administered orally, vitamin C tightly controls the level in the blood, and allows for reaching a peak concentration of 300 μM. But when administered intravenously, this tight control is omitted, and a concentration up to 20 mM can be reached.^{40,41} Based on this, some studies suggested that higher vitamin C levels to be obtained intravenously could provide the effect that could not be provided through oral administration; and that they could also kill cancer cells.³² But no such benefits of intravenous administration of high-dose vitamin C in cancer treatment were observed in well-designed, randomized controlled trials performed later on.^{17,18}

In studies, where the use of high doses of vitamin C in combination with other cancer treatment regimens was assessed, conflicting results were obtained. In a 1/phase 2A study carried out in 2014 on 27 patients with stage 3–4 ovarian cancer, who were divided into 2 groups and treated with either chemotherapy (carboplatin + paclitaxel) or chemotherapy plus high-dose IV vitamin C. As a result, no difference was seen in the group, who received high-dose IV vitamin C, in terms of survival and progression-free survival; but the prevalence of grade 1–2 side effects of chemotherapy decreased significantly. However, no decrease was observed in grade 3–4 side effects that create the main problem in toxicity, and cause disruption of the treatment.⁴² The results of the studies, where the use of high-dose vitamin C in combination with arsenic trioxide were evaluated, were contradictory.^{7,8} It has been seen that the similar combinations have led to serious side effects and have also caused the disease to progress during the treatment also in acute myeloid leukemia, refractory metastatic colon cancer, and metastatic melanoma.^{9,10,26}

In a study published in 2010, where the studies carried out over 33 years were compiled, it was concluded that “whether high-dose Vitamin C has an anti-tumor activity or not, and if any, what doses of Vitamin C is effective on which histological types of cancers are

all unknown”¹⁸ The American Cancer Society states that high-dose vitamin C is introduced as a cancer treatment but the currently available clinical evidence does not show any benefit of high-dose vitamin C.¹⁷ But despite all these, high-dose vitamin C is widely used by practitioners of complementary and alternative medicine. In the surveys conducted during the conferences on complementary and alternative medicine held in 2006 and 2008, 172 of 199 participants reported that they administered high-dose vitamin C to their patients.²⁰

7. Conclusion

In conclusion, for now, there is no clear evidence that high-dose vitamin C is beneficial in the treatment of cancer. Although favorable results have been achieved in some laboratory and animal studies, these assertions have not been supported by clinical studies. With the studies conducted, ascorbic acid administered intravenously made it possible to reach higher concentrations in the blood. Based on this, IV ascorbic acid is more likely to be more effective than oral administration. However, this effect has yet to be proven. In the ongoing studies, researchers are focused on whether IV ascorbic acid may enhance the effectiveness of other cancer treatment regimens such as chemotherapy and radiotherapy. At this point, it is possible to benefit from it, to a certain extent. However, it is better to abstain from this treatment, considering the potential side effects, until the completion of the studies and until its benefits (if any) is clearly demonstrated.

Conflict of interest

The authors declare that they have no conflict of interest.

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