An Insight and Update on the Analgesic Properties of Vitamin C

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ABSTRACT

Pain is an unpleasant subjective feeling having implications on both physical and mental realm. Multiple dimensions of pain involving behavioral, spiritual, emotional, and cognitive changes have been studied and pathways elucidated. It is stressed that the nature in which pain is modulated and perceived at a higher center is a complex phenomenon. One of the main goals of pain modulation is to modify pain to a more tolerable level, rather than its complete eradication. Different pain management interventions were tried but have effects that are more adverse. Till date, the only reliable pain blockers are analgesics and anti-inflammatory drugs in the form of opioids and non-opioids. Despite this, most of the drugs are ineffective at various levels, furthermore, adding to complications. Thus, there is an urgent need for effective intervention with minimal side effects. Ascorbic acid, popularly known as vitamin C, has shown to exhibit promising analgesic properties. The literature is sparse with the usage of the drug in various forms of pain. This review focuses on the dynamics and kinetics of vitamin C and its usage in various forms of pain. With minimal adverse effects, the drug is shown to perform well in different types of pain disorders, thus paving way for alternative interventional agent for pain management.

Keywords: Analgesia, dynamics, vitamin C

INTRODUCTION

Pain is often described as a distressing feeling, unpleasant emotional experience, and a subjective phenomenon.[1] It is a multidimensional phenomenon with sensory, physiological, cognitive, affective, behavioral, and spiritual components, and is experienced by adapting the transmission of unpleasant stimuli to the brain component.[2]

Despite the advances in health care, management of postoperative pain remains a hideous task for health-care providers.[3,4] The postoperative pain remains inadequately treated, and the patient experiencing it further increases the risk for complications by increased duration of hospital stay and slowing of rehabilitation process with delay in return to regular functions, which is supported by various studies.[5-7]

The total amount spent on pain management per annum was greater than the amount spent on heart diseases, cancer, and diabetes.[8] Melzack and Wall[9] through “gate theory of pain” showed how the pain modulation techniques take advantage of body’s endogenous pain-modulating abilities. One of the main goals of pain modulation is to modify pain to a more tolerable level, rather than its complete eradication. This goal can be accomplished by an array of modalities such as pharmacological and non-pharmacological interventions.[9] Pharmacological interventions include nonsteroidal anti-inflammatory drugs (NSAIDs) such as antidepressants, anticonvulsants, invasive pain modulators, and invasive pain relievers. Non-pharmacological interventions include behavioral modification procedures such as relaxation, music therapy, and distraction, and pain modulators

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such as transcutaneous electrical nerve stimulation, acupuncture, and conditional exercises as well.

Different ways of pain management have been tried with varying degree of success. To date, only opioid and non-opioid analgesics are considered for reducing pain arising from various oral and non-oral inflammatory pathoses. Nevertheless, they have limitations in the usage, based on the clinical condition of the individual and the adverse effects associated with them. With increased concerns over poor efficacy and abuse of opioids, there is a clear necessity for alternative approaches that can be safe and efficient to pharmacotherapy. Studies have shown that vitamin C exhibits analgesic properties and proves to have potential role in the improvement of quality of life in the patients having oro-dental pathosis, complex regional pain syndrome (CRPS), and cancer interventions. This review was carried out with an intention to explore and provide insights into the analgesic role of vitamin C.

**DATABASE SEARCH FOR POTENTIAL STUDIES ON ASCORBIC ACID AND ANALGESIA**

A literature search was carried out in search databases such as EBSCO, PubMed, Google Scholar, and ResearchGate. The MeSH keywords used in the search were “vitamin C,” “ascorbic acid,” “analgesia,” “pain relief,” “neuropathic pain,” and “dental pain” from the year 1980 to 2017.

Randomized controlled trials only were considered. The search was confined to those studies that incorporated ascorbic acid in oral or injectable forms as a primary drug for pain in various pain disorders compared with placebo. Articles in any language other than English, having only abstracts, presentation of case reports, and multiple therapeutic usage of antioxidants or micronutrients as well as systematic reviews were excluded.

Various studies involving the usage of vitamin C as analgesia have been highlighted in Table 1.

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart of the studies retrieved and considered for the analysis have been represented in Table 2.

**DYNAMICS AND KINETICS OF VITAMIN C**

Vitamin C, also known as ascorbic acid or ascorbate, is a six-carbon lactone, which is synthesized from glucose via the glucuronic acid pathway in animals. During evolutionary process, the biosynthetic capacity of ascorbate in highly evolved species was lost because of genetic defect, causing the lack of L-gulonolactone oxidase, which is a terminal enzyme in the biosynthetic pathway.

Therefore, humans totally are dependent on dietary intake of this vitamin. Unlike humans, mice and rats can synthesize vitamin C. This defect in the pathway of biosynthesis of vitamin C was first elucidated by CG King (USA), BC Guha (India), LW Mapson (England), and coworkers. According to Chatterjee, this lack of vitamin C production because of mutational defects made humans to rely on external supplements. It is present in various foods, mainly of plant origin, typically in the quantities of 10–100 mg/100 g. Interestingly, the process of ascorbate biosynthesis follows different pathways in animals, plants, and fungi. In plants, it starts with guanosine diphosphate-D-mannose, which is then converted to L-galactonolactone, a substrate for the plant homolog of L-gulono-1,4-lactone oxidase, L-galactonolactone dehydrogenase. But in yeasts, it is D-erythroascorbate, a C2 analog of ascorbate, which proceeds from D-arabinose.

Vitamin C is as an essential component for collagen synthesis, and being an essential component of connective tissue, it plays an important role in the process of wound healing. As a well-documented antioxidant, it is capable of stabilizing and reducing reactive oxygen species (ROS), by scavenging factors that promote inflammation in the dermis. Vitamin C also plays a vital role in the immune function by improving the absorption of nonheme iron. Moreover, it also involves in vascular remodeling as well as in the maintenance of integrity of vascular cell by influencing the differentiation of vascular smooth muscle cells and the expression of connective tissue proteins.

A study conducted by Leboy et al. had shown that ascorbate produced effects on bone cells both in vitro and in vivo, through promoting gene expression, thereby involving in the differentiation of chondrocytes. Ascorbate showed dual functions, that is, both stimulatory and inhibitory effects on the osteoclast genesis in vitro. Some studies have reported that ascorbate significantly increased the number, size, and nucleation in primary mouse bone marrow cultures. However, when they were treated with ascorbate, the late-stage osteoclasts in culture initiated cell death. Yet, few authors observed the reversal of osteoclastic activity following the treatment of rats with ascorbate, which increases glutathione concentrations. Further, it also proved the role of vitamin C as an antioxidant, and more of its action in preventing osteoclastic differentiation rather than in promoting osteoblastic activity.

**RECOMMENDED DIETARY ALLOWANCES**

Food and Nutrition Board (2000) at the Institute of Medicine of the National Academies developed...
Table 1: Investigational studies on vitamin C and analgesia

| S. no | Year | Title of publication | Authors | Methodology | No. of patients | Inference |
|-------|------|----------------------|---------|-------------|----------------|-----------|
| 1.    | 2016 | Effect of intravenous high-dose vitamin C on postoperative pain and morphine use after laparoscopic colectomy: a randomized controlled trial | Jeon et al. | Randomized placebo-controlled trial to examine the effect of high-dose vitamin C (50 mg/kg) on postoperative opiate consumption and pain scores in patients with colon cancer. Postoperative fatigue and side effects were analyzed as secondary outcomes | A total of 100 patients were enrolled and allocated to receive 50 mg/kg vitamin C | High-dose vitamin C infusion decreased postoperative pain during the first 24 h and also reduced morphine consumption in early postoperative period |
| 2.    | 2016 | Effect of intravenous vitamin C on postoperative pain in uvulopalatopharyngoplasty (UPPP) with tonsillectomy | Ayatollahi et al. | Randomized double-blinded clinical trial. The study investigated the analgesic effects of vitamin C in patients undergoing UPPP and tonsillectomy | Forty patients within the age range of 25–30 years and with body mass index <35 | Administration of 3-g vitamin C intravenously during intraoperative reduced postoperative pain without any increased side effects |
| 3.    | 2012 | Effect of vitamin C on morphine use after laparoscopic cholecystectomy: a randomized control trial | Kanazi et al. | Randomized double-blinded placebo-controlled trial to assess the role of single prophylactic dose of vitamin C (2 g po) in reducing the consumption of opioids postoperatively | Eighty adult patients received 2 g vitamin C po or placebo | Supplementation with vitamin C (2 g po) reduced morphine consumption in the postoperative period in the patients who underwent cholecystectomy |
| 4.    | 2007 | Can vitamin C prevent complex regional pain syndrome in patients with wrist fractures? A randomized, controlled, multicenter dose–response study | Zollinger et al. | A dose–response study was designed to evaluate protective effect of vitamin C in the patients with wrist fractures. The effect of gender, age, fracture type, and cast-related complaints on the occurrence of complex regional pain syndrome was also analyzed | Double-blind, prospective, multicenter trial, 416 patients with 427 wrist fractures were randomly allocated | Vitamin C reduced the prevalence of complex regional pain syndrome after wrist fractures and they recommended a daily dose of 500 mg for 50 days |
| 5.    | 2003 | Reduced pain from osteoarthritis in hip joint or knee joint during treatment with calcium ascorbate. A randomized, placebo-controlled crossover trial in general practice | Jensen | The trial was a multicenter, double-blinded, randomized, placebo-controlled, crossover trial performed to examine the effect of vitamin C on human osteoarthritis | One hundred and thirty-three patients with radiographically verified symptomatic osteoarthritis of the hip joints and/or the knee joints were treated with 1 g of calcium ascorbate or identically looking placebo tablets | Acceptable intake of vitamin C would be of importance considering the large prevalence of osteoarthritis |
| 6.    | 2017 | The association of dietary vitamin C intake with periodontitis among Korean adults | Lee et al. | Korean population-based study stated insufficient intake of dietary ascorbic acid was associated with increased periodontitis | In this cross-sectional study, 10,930 adults from the fourth Korean National Health and Nutrition Examination Survey data were analyzed for periodontitis and dietary vitamin C intake | Inadequate dietary vitamin C intake was associated with periodontitis among Koreans |
| 7.    | 2003 | Clinical management and control of alveolalgia (“dry socket”) with vitamin C | Halberstein and Abrahmsohn | Four grams of vitamin C were administered in 25 dental extraction individuals having dry socket and investigated for their healing course among 696 people | A total of 3.5% of the individuals were females and were from low socioeconomic background | The individuals treated with vitamin C showed rapid recovery among 696 extractions |
dietary intake references for the intake of vitamin C and other nutrients.[29] Currently, the recommended dietary allowance (RDA) is 90 and 75 mg/day for adult male and female, respectively. The range for children and infants was provided depending on the age and sex, that is, 15–65 mg/day for children and 40–50 mg/day for infants.[29] In case of adults, increased intakes of RDA were recommended for pregnant women, lactating women, and smokers as well.

**INTERFACES OF PAIN AND VITAMIN C**
Clinical research in terms of pain and vitamin C deficiency remains limited and needs further exploration. Nevertheless, so far, the available research has shown the potential of vitamin C in relation to the chronic pain states and associated comorbidity.

A report stated that the acute deficiency of vitamin C leads to scurvy, and the development of symptoms depends on the depletion of vitamin stores in body or low intake of vitamin C, which is below 10 mg/day.[30] Symptoms of its deficiency include fatigue, malaise, and inflammation of gums, and as it progresses, it affects the collagen synthesis leading to its depletion and weakening of connective tissues causing petechiae, ecchymoses, joint pain, poor wound healing, iron deficiency, and hyperkeratosis.[31-33]

**NEED FOR INTERVENTIONS FOR PAIN MODULATION**
Pain modulation refers to the process by which the body alters a pain signal when it transmits along
the pain pathway and explains, at least in part, why the individual’s response to pain stimulus differs at times.[34] Through pain modulation, there might be either enhancement or inhibition of painful messages that travel from noxious receptors to central nervous system. This process happens at every level of pain pathway such as spinal cord, brain stem, and the cortex. A nationwide study reported that the prevalence of hypovitaminosis C is high in the general population, and the results highlighted the association between vitamin C and spinal pain, thereby warranting further investigations.[35,36]

**Vitamin C and Mode of Analgesic Actions via Neuronal Mechanism**

Although unclear, vitamin C primarily exerts its antinociceptive effects mainly based on its antioxidant properties by scavenging a wide range of ROS and thereby protecting cells and tissues as well as nerves from oxidative damage.[36-39]

A recent study by Schencking et al.[11] in 2012, also revealed lower plasma concentrations of vitamin C in the patients with postherpetic neuralgia than in healthy individuals, and thereby, when those patients were treated with vitamin C, spontaneous pain decreased by its role in the synthesis of collagen, neurotransmitters, and numerous peptides. Similarly, in CRPS, following an orthopedic surgery, there was a significant reduction in its effectiveness to be less when compared to NSAIDs.

A case report also described that the infusion of vitamin C was effective in zoster-associated neuralgia.[41] Conversely, Jensen et al.[43] administered oral 1-g calcium ascorbate per day for 2 weeks in the patients with osteoarthritis of hip or knee joint, and found out its effectiveness to be less when compared to NSAIDs. But when given in the form of infusions of high-dose vitamin C in a patient with rheumatoid arthritis, it produced complete decrease in pain.[43]

The effectiveness of intravenously administered vitamin C on acute pain in the patients with herpes zoster infection was evaluated, and it was concluded that its administration was effective for reducing the incidence of post herpetic neuralgia by modulating serum levels of cytokines, interleukin (IL)-6 and IL-8.[10-12]

**Vitamin C in Oncological Practice**

The protective role of vitamin C against cancer was first hypothesized in the 1950s, but Cameron and Pauling in the 1970s, suggested its therapeutic effect in their report. Increased survival in the patients with advanced cancer was observed when treated with intravenous (IV) vitamin C.[44,45] In contrast, when higher doses of oral vitamin C were tested, it failed to produce similar benefits when compared to IV infusions.[46,47]

Suggestive evidence from past research has shown that vitamin C played an effective role in pain reduction in the patients with cancer and further, in improving their quality of life. When large doses of vitamin C were administered in the patients with terminal cancer, prolonged survival rates were observed with significant decrease in the subjective symptoms such as pain and also the need for analgesics.[45,49] A study was carried out to quantify the effect of high-dose vitamin C on pain and cancer-related symptoms using European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire.[50] It was found that vitamin C was effective in decreasing pain, and also was safe and tolerable.[51-53]

Even though, cancer-related pain could typically be managed by opioids, studies have shown that intake of high-dose vitamin C has significantly decreased the opiate dependence.[45] In another study by Carr et al.,[54] where parenteral vitamin C was given, they observed complete decrease in morphine requirement in a patient with terminal cancer. Moreover, no side effects were found following the intake of vitamin C in the treatment. The effect of high-dose vitamin C (50 mg/kg) along with opiate consumption postoperatively in the patients with colon cancer showed that the vitamin C infusion decreased postoperative pain during the first 24h and reduced the consumption of morphine in early postoperative period.[13]

**Vitamin C and Dentistry**

Vitamin C (L-ascorbic acid) is a well-known micronutrient with its anticorbutic activity. Ascorbic acid deficiency had been exclusively implicated in the causation of scurvy. The incidence of scurvy has since then diminished in the population because of prescription of the vitamin as a dietary micronutrient.[55]

A Korean population-based study stated that insufficient intake of dietary ascorbic acid was associated with increased periodontitis pain.[56] Studies and literature on vitamin C usage in extraction sockets, oral mucositis, and oral ulcers not related to scurvy are sparse. However, a study in this direction showed that the supplemental vitamin C therapy was associated with rapid recovery in 696 individuals undergoing dental extraction.[57]

**Recommendations**

Accumulating evidence from literature has shown that vitamin C has its potential role in antinociceptive...
effect and postoperative pain relief. In addition, future trials are needed to further explore its potential effect on postoperative pain following tooth extractions, treatment of oral ulcers, and its optimal doses and routes of administration.

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Conflicts of interest
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