Use of Oral Vitamin C After Fractures of the Distal Radius

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THERE HAS BEEN considerable debate regarding the effect of vitamin C on the prevention of complex regional pain syndrome (CRPS) in the setting of distal radius fractures.[1–3] Vitamin C, also known as ascorbic acid, is a water-soluble organic compound first identified in 1932. Although humans are unable to synthesize vitamin C, it is an essential micronutrient in many enzymatic and chemical pathways. Vitamin C acts as a cofactor for 8 different enzymes that are involved in collagen hydroxylation, carnitine and norepinephrine biosynthesis, amidation of peptide hormones, and tyrosine metabolism.[4] In addition, vitamin C acts as a powerful chemical reducing agent, or antioxidant.[4]

Vitamin C is found in a large number of vegetables and fruits (Table 1).[5] The precise amount of vitamin C in a specific vegetable or fruit varies based on serving size, season, transport, shelf time, storage, and cooking practices. If an individual consumes 5 standard servings of vegetables and fruit in a day, daily vitamin C intake will range from 210 to 280 mg.[4]

Complex regional pain syndrome, also known as reflex sympathetic dystrophy or algodystrophy, occurs frequently after fracture of the distal radius. Although reported incidence varies from one study to another, the incidence has been reported to be as high as 25% to 37% in prospective investigations.[6,7] CRPS is characterized by unexplained pain and swelling, vasomotor instability, and loss of joint mobility. The pathophysiology of CRPS remains poorly understood.

Two landmark, randomized, controlled trials by Zollinger et al. demonstrated that vitamin C reduces the incidence of CRPS in the setting of distal radius fractures.[1,2] In the most recent trial, 416 patients with 427 wrist fractures were randomized to treatment with placebo or treatment with 200, 500, or 1500 mg of vitamin C daily for a period of 50 days. The prevalence of CRPS type I was 10.1% in the placebo group and 2.4% in the vitamin C group (p=.002). Patients were diag-

TABLE 1. Food Sources of Vitamin C

Food Source (Preparation, Portion Size)	Vitamin C (mg)	Calories
Fruits		
Cantaloupe (raw, ¼ medium)	47	51
Guava (raw, ½ cup)	188	56
Kiwi (raw, 1 medium)	70	46
Mango (raw, ½ cup)	23	54
Orange (raw, 1 medium)	70	62
Papaya (raw, ¼ medium)	47	30
Pineapple (raw, ½ cup)	28	37
Strawberries (raw, ½ cup)	49	27
Vegetables		
Broccoli (cooked, ½ cup)	37	26
Broccoli (raw, ½ cup)	39	15
Brussels sprouts (cooked, ½ cup)	48	28
Cauliflower (cooked, ½ cup)	28	17
Edible pod peas (cooked, ½ cup)	38	34
Green pepper (sweet, cooked, ½ cup)	51	19
Green pepper (sweet, raw, ½ cup)	60	15
Kale (cooked, ½ cup)	27	18
Kohlrabi (cooked, ½ cup)	45	24
Red sweet pepper (cooked, ½ cup)	116	19
Red sweet pepper (raw, ½ cup)	142	20
Sweet potato (canned, ½ cup)	34	116
Juices		
Grapefruit juice (¾ cup)	50–70	71–86
Orange juice (¾ cup)	61–93	79–84
Tomato juice (¾ cup)	33	31
Vegetable juice cocktail (¾ cup)	50	34

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nosed with CRPS type I if 4 of the 5 criteria suggested by Veldman et al. were present at the hand or wrist: unexplained diffuse pain, difference of skin color relative to the contralateral side, diffuse edema, difference in skin temperature relative to the contralateral side, and limited active range of motion.[8] A beneficial dose–response was observed; however, the effect reached a plateau at a dose of 500 mg per day. A statistically significant difference was not observed between the placebo group and the 200-mg group, suggesting that typical dietary intake alone may be insufficient in the prevention of CRPS. Independent investigation of the role of vitamin C in the prevention of CRPS would significantly add to the existing literature.

EDUCATIONAL OBJECTIVES

- Describe the mechanism of actions for Vitamin C
- State the role of Vitamin C in the prevention of CRPS
- List the appropriate dose of daily Vitamin C
- Define the role of Vitamin C after distal radius fracture

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Concerns have been raised regarding the methodology of the 2 trials conducted by Zollinger et al.[3,9,10] One issue is the confounding effect of cast complaints. Patients with early cast complaints were far more likely to develop CRPS (relative risk, 5.35).[2] However, the primary concern revolves around the diagnosis of CRPS. Although the 2 trials used the diagnostic criteria suggested by Veldman et al.,[8] there are alternative sets of criteria published in the literature. The lack of consistency among these sets of criteria indicates that the exact nature of CRPS remains uncertain, and its diagnosis imprecise. Owing to a lack of precision in the diagnosis of CRPS, Zollinger et al. acknowledged that whereas vitamin C ameliorates the Veldman signs and symptoms, it may not prevent CRPS.[2]

In addition, there is a lack of clarity regarding the mechanism by which vitamin C acts to decrease the incidence of CRPS.[3] Toxic oxygen radicals are thought to be involved in the pathogenesis of CRPS,[11] and their production in neutrophils is reduced in the presence of vitamin C.[12] The role of vitamin C has been studied in other inflammatory processes. In the setting of burns, vitamin C serves as a scavenger of free oxygen radicals. In addition, there are data supporting vitamin C's role as an antioxidant in limiting skeletal muscle injury caused by ischemic reperfusion injury or compartment syndrome.[13,14] One can infer that there may be a similar physiologic basis for vitamin C in the prevention of CRPS.

Beyond its role in the prevention of CRPS, vitamin C is integral to collagen formation and bone synthesis. Rodent studies have consistently demonstrated a beneficial effect from vitamin C supplementation during the fracture healing process.[15–18] In addition to accelerating the fracture healing process,[15,16] vitamin C supplementation improves the mechanical resistance of the developing fracture callus.[18] Free oxygen radicals impair fracture healing and are produced naturally by the inflammatory process surrounding a fracture. The antioxidant properties of vitamin C neutralize the adverse effects of free oxygen radicals.[17] The effect of vitamin C on fracture healing has not been studied thoroughly in humans. One study demonstrated that conservatively treated tibial shaft fractures healed 3 weeks earlier when supplemented with vitamin C.[19] However, the study suffered from a high attrition rate and an inability to control for multiple confounding variables. Overall, the literature analyzing the effects of vitamin C on the fracture healing process in humans is inadequate to make any absolute recommendations on its use.

Although controversy exists regarding the value of prescribing vitamin C to patients with distal radius fractures, there appears to be limited downside with its use. Adverse effects of vitamin C are dose-dependent and occur at doses well above the recommended daily allowance of 60 mg daily. Generally, adverse side effects can be avoided with doses below 1000 mg daily in healthy people.[4] When several grams of vitamin C are taken at once, diarrhea and abdominal bloating are the most frequent side effects. In addition, renal calculi can precipitate as a result of the ingestion of excess vitamin C. Oxalic acid is produced and renally excreted during vitamin C metabolism. In patients with underlying hyperoxaluria, oxalate excretion is accelerated with vitamin C doses above 1000 mg daily and can contribute to formation of renal calculi. Similarly, hyperuricosuria can occur with large doses of vitamin C, also leading to formation of renal calculi. In patients requiring dialysis, hyperoxalemia can occur with doses as low as 500 mg daily. Therefore, these patients should limit daily intake to 200 mg.

Based on the existing literature, patients with distal radius fractures should be treated with vitamin C to limit the risk of developing CRPS. Specifically, a daily dose of 500 mg for a period of 50 days is recommended. Dietary intake alone is insufficient. There may

be an incidental benefit of reduced time to fracture healing, although this potential benefit merits further clinical investigation. The disadvantages of treatment with vitamin C are trivial given its low cost and limited side effect profile with doses less than 1000 mg daily. The use of vitamin C does not obviate the need for careful splinting and casting, which also has a role in the development of CRPS.

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