Is the Use of Supplemenal Vitamin C and Zinc for the Prevention and Treatment of Pressure Ulcers Evidence-Based?

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Supplemental zinc and vitamin C are routinely prescribed for the prevention and treatment of pressure ulcers. The authors sought to determine whether there is sufficient evidence-based medical research to support the use of these supplements. Both zinc and vitamin C have been shown in animals to be necessary for effective wound healing. Since malnutrition in institutionalized older patients may contribute to their risk of developing pressure ulcers and may interfere with the treatment of these lesions, it has been proposed that improving nutrition through supplementation of vitamin C and zinc may assist in the prevention and treatment of pressure ulcers. However, the authors' review of the literature found that there is insufficient evidence to support the routine use of supplemental zinc and/or vitamin C in individuals with adequate nutrition. Furthermore, supplemental zinc may produce a number of adverse effects. (Annals of Long-Term Care: Clinical Care and Aging 2010;18[3]:28-32)

Introduction

There are several types of skin ulcers that affect older patients: venous or stasis ulcers, arterial insufficiency ulcers, diabetic neuropathic ulcers, and pressure ulcers. In this article, we will focus on whether zinc and vitamin supplementation assist in wound healing, with the focus on pressure ulcers, also referred to as decubitus ulcers, pressure sores, and bedsores.

Epidemiology

Before discussing the incidence and prevalence of pressure ulcers, it is important to point out that there are few good nationwide studies. Pressure ulcers are estimated to affect 1.3-3.5 million people in the United States. Older people account for 70% of all pressure ulcers. The highest incidence of pressure ulcers has been reported in hospitalized vulnerable elderly persons undergoing orthopedic procedures (9-19%) and quadripleges (33-60%). In response to a challenge from the National Pressure Ulcer Advisory Panel (NPUAP), a survey was conducted from 1989 to 2005. The survey included 148 U.S. health facilities. The range of pressure ulcer prevalence prior to 1999 was from 9.2% to 11.1%. Over the next six-year period, from 1999-2005, the prevalence of pressure ulcers remained at 15%. Similarly, the European Pressure Ulcer Advisory Panel (EPUAP) has reported prevalence rates ranging from 8-23%. Studies conducted in the Netherlands have shown the prevalence of pressure ulcers to range from 12.8-20.3% in one study and 23.1% in another.

The incidence of these lesions in intensive care units (ICUs) is reported to range from 14% in short-stay units to as high as 41% in long-stay units. In a cross-sectional point study done in Dutch ICUs, the national prevalence rate was as high as 28.7%. A survey of four European countries has reported a prevalence of 4% in Denmark and as high as 49% in Germany. In East Carolina, the prevalence rate prior to implementation of a prevention program in two ICUs was 11.7%. Another study done in an ICU in a midwestern U.S. hospital showed that 20% of the patients developed pressure ulcers during their ICU stay.

Prevalence of pressure ulcers is also higher in the elderly, in those who are acutely ill, and in persons with spinal cord injury. In a review done over a six-year period in participating acute care healthcare organizations in the United States, prevalence rates ranged from 14-17%. Over a 10-year period from 1990 to 2000, the NPUAP reported that the prevalence in acute care settings ranged from 10-18%, 2.3-28% in long-term care (LTC), and 0-25% in home care. Another study found a prevalence of 11.4% in 10,000 nursing home (NH) residents. In 2004, the Center for Medicaid and State Operations reported a prevalence of 9.1% in NHs. Variations in sample characteristics and study methodologies, and difference in the range of prevalence, make it necessary to interpret these results with caution.

Pressure ulcers are seen by healthcare professionals as a quality indicator. The first regulation to be revised by the Centers for Medicare & Medicaid Services (CMS) was on pressure ulcers. This is based on the belief that the current rate of pressure ulcers in LTC facilities can be significantly reduced with appropriate intervention. The
Evidence shows that improved nutrition and protein supplementation may assist in the prevention and successful treatment of pressure ulcers.

Malnutrition and Pressure Ulcers

The impetus for the frequent administration of supplemental zinc and vitamin C may be the frequent occurrence of malnutrition in LTC facilities. Malnutrition appears to be a risk factor for pressure ulcers.\textsuperscript{35-36} Malnourished patients have approximately two times greater risk of developing pressure ulcers than normally nourished patients.\textsuperscript{37} Malnutrition may negatively impair the prevention and successful treatment of pressure ulcers.\textsuperscript{36-37} The incidence of pressure ulcers is increased in patients with decreased protein and energy intake.\textsuperscript{35-38} This relationship has also been observed in animal models where severe protein-energy malnutrition increases infection in wounds, decreases collagen deposition, and reduces tensile strength.\textsuperscript{41} The percentage intake of dietary protein has also been found to predict development of pressure ulcers.\textsuperscript{35} Evidence shows that improved nutrition and protein supplementation may assist in the prevention and successful treatment of pressure ulcers.\textsuperscript{35-39}

Studies have shown the benefit of treatment with high-protein dietary supplements for 15 days and a high-calorie diet in decreasing pressure ulcers.\textsuperscript{39} However, other studies have failed to confirm a causal relationship between nutrition interventions and the development of pressure ulcers. A review of seven studies of the relationship between malnutrition and pressure ulcers found no association between the two.\textsuperscript{41} One study did show a positive effect of nutritional supplementation in critically ill inpatients with regard to pressure ulcers. However, the difference in incidence was very small (41\% vs 47\%).\textsuperscript{42} Reviewing all the evidence available is beyond the scope of this article; however, based on the current evidence available, a causal relationship between malnutrition and the development and/or failure of the treatment for the pressure ulcers remains to be established. The recent Cochrane Review on nutritional interventions in pressure ulcers found no evidence that mixed nutritional supplements reduce the chance of pressure ulcer development in a critically ill elderly patient. Overall, studies have been inconsistent, of small sample sizes, or using poor-quality methods.\textsuperscript{43}

Vitamin C

The use of vitamin supplementation to accelerate wound healing is even more controversial than that of higher pro-
protein intake. One of the earliest studies of ascorbic acid (AA) for the treatment of pressure ulcers was a double-blind, placebo-controlled trial of 20 patients in a surgical ward who were followed for one month. In patients receiving supplementation with AA 500 mg, the healing rate of pressure ulcers was double that of patients receiving placebo. Six of the AA-treated patients had complete healing of their wounds. This landmark study probably spurred the increased prescription of vitamin C for wound healing. In 1995, another study was done involving 11 NHs and one hospital, in which 88 patients were randomized. The intervention group received AA 500 mg twice daily, with or without ultrasound, for 12 weeks. The control group was given AA 10 mg twice daily (one-third of the recommended dietary allowance (RDA)). The results of this study were inconclusive. The main outcomes were surface reduction, healing velocity, and volume reduction of the wounds over 12 weeks. The study could not detect a higher healing rate by any of these measures in the treatment group. These results did not support the use of AA supplementation to accelerate healing of pressure ulcers.

The study of vitamin C and pressure ulcers done by Taylor et al. in 1974 included only 20 patients. It is not clear whether the patients were truly randomized. Even though they found significant reduction of pressure sore area, the clinical significance of this as opposed to wound healing is unclear. The study done in 1995 by ter Riet was mainly based on NH patients. It was also noted that most had nutritional deficiencies on admission. Despite the large sample size, it was still unclear what the role of vitamin C is in pressure ulcer treatment.

The Cochrane review was able to find only two studies reviewing the role of vitamin C in pressure ulcer treatment, and neither one of them was conclusive. The current evidence does not support the routine use of vitamin C supplementation in the absence of scurvy in patients with pressure ulcers.

Zinc

The data for zinc supplementation in patients with pressure ulcers are very scarce. Currently, there is no evidence to support the use of zinc in patients with normal zinc levels and pressure ulcers. Most studies done on zinc supplementation utilize plasma zinc levels to quantify deficiency. This zinc is bound to plasma protein. Plasma zinc levels are homeostatically regulated and are affected by other factors. Serum levels do not necessarily correlate with tissue levels. Studies have also found it difficult to deplete humans of zinc because of this excellent homeostasis.

Other methods of measuring zinc include excretion with urine, zinc content in erythrocytes and leucocytes, and free zinc level in cells and serum. Unfortunately, one single test cannot accurately determine true zinc level. Currently, a plasma zinc level under 60 μg/dL is considered a deficiency. Developing a test to accurately measure zinc status in tissue is a challenge at the present time. For clinical purposes, one would have to show a decreased content of zinc in serum, lymphocytes, and erythrocytes, along with clinical signs and symptoms associated with zinc deficiency. These would further need confirmation with a zinc tolerance test. Serum zinc levels also decrease with age, thus a low serum level could be a physiological part of aging. All of these factors make the results of studies associating zinc deficiency with pressure ulcers unreliable, since none of the studies were accurately able to determine zinc deficiency in patients with pressure ulcers. It is therefore not surprising that zinc supplementation has not shown clinically significant improvement in pressure ulcer healing.

Norris and Reynolds conducted a randomized, double-blind study in 1971 of 14 patients with pressure ulcers. The groups were randomized to receive zinc sulfate 200 mg 3 times a day or placebo for 4 weeks; the groups were switched after 12 weeks. It was not clear how the patients were allocated. Only 3 of the 14 patients completed the study after 24 weeks, so this trial is limited by the small number of patients. No significant effect of zinc was seen on the pressure ulcers; however, no interpretation of clinical significance can be made because of the small number of patients.

A randomized controlled study was done in France using a dietary supplement that included zinc. The study looked at 672 people over the age of 65 years. The difference in pressure ulcers was statistically significant: 41% versus 47% in the control group. However, the difference was relatively small and could not be attributed to zinc alone. There were also issues regarding the design of the study and data interpretation.

Another small study showed significant reduction in wound area, amount of exudates in infected ulcers, and improvement in wound condition in patients with stage III and IV pressure ulcers receiving supplementation with arginine, vitamin C, and zinc combination. The study could not conclude whether the improvement was a direct result of supplementation with zinc or vitamin C individually. Studies show that zinc is necessary for normal protein metabolism and wound healing, but routine supplementation appears to provide no additional benefit in pressure ulcers, and may in fact be harmful. Currently, there is no evidence to support the routine use of high doses of zinc supplementation in patients with pressure ulcers.

Adverse Effects

It is important to examine possible downsides of zinc and vitamin C supplementation. The RDA for vitamin C in adults in the United States is 60 mg per day. This is based on the minimum requirement needed to prevent
scurvy. The recommendation for the United States is two standard deviations above the average intake needed to provide adequate stores. In addition, it appears that elderly persons do not require a higher quantity than their younger counterparts. The maximum recommended amount of vitamin C per day is 2000 mg. Many people take higher amounts of vitamin C for viral infections or atherosclerosis. Even though vitamin C is considered nontoxic, higher-than-recommended doses of vitamin C can cause problems. Common side effects may include nausea and diarrhea, acidification of the urine, and interference of the antioxidant-prooxidant balance in the body. Serious side effects could possibly include oxalate acid stones in patients prone to oxaluria. Uricosuria and uric acid stones can also occur. Patients with a deficiency of the enzyme glucose-6-phosphate dehydrogenase can go into a hemolytic crisis. Patients with thalassemia or hemochromatosis who are given megadoses of vitamin C will mobilize more iron for chelation, which can result in tissue damage.

The RDA for zinc is 15 mg of elemental zinc per day. Zinc sulfate is available on the market in doses of 110 mg and 220 mg, which contain 25 mg and 50 mg of elemental zinc, respectively. Acute zinc toxicity is rare; however, chronic use can have adverse effects. Routine high-dose zinc supplementation can cause copper deficiency, which can result in anemia and neutropenia. Other toxic effects of zinc in large doses include immunosuppression and gastrointestinal distress.

The adverse effects of zinc excess have been studied in 70 institutionalized patients receiving high-dose oral zinc supplementation for the promotion of the healing of pressure ulcers. While zinc showed no beneficial effects on the healing of pressure ulcers, it did produce a 7.8 times greater risk of antibiotic requirement for infections in the group receiving zinc sulfate. Patients receiving zinc supplementation were also 12.5 times more likely to have gastrointestinal side effects. These results indicate that in institutionalized older people with pressure ulcers, high doses of routine zinc supplementation can lead to clinically significant adverse effects with little benefit. Therefore, zinc supplementation in patients without a deficiency is not recommended.

Our Recommendations

Guidelines from the Agency for Healthcare Research and Quality (AHRQ), American Medical Directors Association, and the Consortium for Spinal Cord Medicine all recommend nutritional support for the prevention and healing of pressure ulcers. The AHRQ guidelines recommend that patients with pressure ulcers should first be assessed for nutritional deficiencies. Nutritional support should then be based on these deficiencies and individualized for each patient. Therefore, routine vita-

A simple daily vitamin or two daily supplemental drinks appear to be adequate for elderly persons recovering from acute illnesses.

min C and zinc supplementation in pressure ulcers is not indicated. A Cochrane review in 2003, updated in 2008, showed conflicting data on vitamin C and zinc supplementation in pressure ulcers. So far, no consistent acceleration in wound healing has been reported with vitamin C or zinc supplementation in patients with pressure ulcers.

Most clinical trials of supplements of vitamin C and zinc have either been on small numbers of patients or have been of poor methodology. There are no true randomized controlled trials for either vitamin C or zinc supplementation for pressure ulcers. Inherent problems with evaluation of zinc levels in the tissues have been identified. Based on the literature, there appears to be no effect of these supplements on prevention or treatment of pressure ulcers.

We recommend a thorough nutritional assessment of patients at risk for pressure ulcers and/or who have pressure ulcers. Caloric, protein, vitamin, and/or mineral supplementation should be considered if there is evidence for deficiencies of these nutrients. A simple daily vitamin or two daily supplemental drinks appear to be adequate for elderly persons recovering from acute illnesses. While vitamin C and zinc appear to be important for the pathophysiology of wound healing, there is insufficient evidence at this time to support the routine usage of higher than the recommended daily allowance for these supplements for the prevention and/or treatment of pressure sores. Better-designed studies are needed to accurately identify patients with pressure ulcers who will truly benefit from higher doses of vitamin C or zinc supplementation.

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References
