Effectiveness of Prophylactic Vitamin C Supplementation in Preventing Complex Regional Pain Syndrome After Distal End Radius Fractures in Older Adults

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Abstract: Background: The effectiveness of vitamin C in preventing complex regional pain syndrome (CRPS) has been debated. This study aimed to assess whether vitamin C can prevent CRPS-1 following distal end radius fractures in older adults.

Methods: This prospective, randomized study involved patients who underwent either conservative or surgical treatment for distal end radius fractures. They were divided into two groups: one receiving vitamin C (500 mg/day) alongside standard therapy and the other receiving only standard therapy for 3 months. CRPS-1 was diagnosed using the Budapest criteria.

Results: CRPS-1 occurred in 11.3% of the vitamin C group compared to 26% in the standard therapy group. The use of vitamin C was significantly linked to a lower likelihood of developing CRPS-1.

Conclusion: Supplementation with vitamin C (500 mg/day) was effective in reducing the incidence of acute CRPS-1. It presents a promising preventive strategy for CRPS-1 after distal end radius fractures.

Keywords: Vitamin C, complex regional pain syndrome, fracture, distal end radius, aging, wrist

INTRODUCTION

Complex regional pain syndrome (CRPS) is a condition affecting the extremities, marked by pain, swelling, limited motion, vasomotor instability, skin changes, and bone loss. It often follows trauma, surgery, or vascular events like strokes. Initially reported in 1865 during the American Civil War, it was known as "causalgia." Over time, it has been called Sudeck’s atrophy and reflex sympathetic dystrophy, among other names. In 1994, the International Association for the Study of Pain (IASP) officially adopted the term CRPS.

CRPS involves chronic pain that is disproportionate to the initial injury and includes sensory, autonomic, and motor disturbances, leading to significant functional impairment and reduced quality of life. There are two types of CRPS: CRPS-1, without nerve damage, and CRPS-2, with nerve damage. Despite this distinction, there is no substantial difference in pathophysiology or treatment response between the types. Most CRPS cases after fractures are classified as CRPS-1.

CRPS-1, more common and without nerve lesions, involves pain, autonomic dysfunction, inflammation, and impaired function. It is particularly severe when linked to fractures, such as wrist fractures, with incidence rates ranging from 1% to 37%. The exact cause of CRPS-1 is unclear, complicating diagnosis and treatment. Current treatments are mainly symptom-based, highlighting the need for preventive strategies.

Vitamin C, an antioxidant, has shown potential in preventing CRPS-1 by neutralizing reactive free radicals thought to be involved in the condition. Studies have shown mixed results on its efficacy in preventing CRPS-1 following distal...
radius fractures. Ongoing research continues to evaluate the effectiveness of vitamin C, especially in the elderly population.

**Material and Methods**

This open-label, prospective, randomized, parallel design study evaluated the effectiveness of vitamin C in preventing CRPS in patients with distal radius fractures. Conducted at a tertiary care teaching hospital in Navi-Mumbai, India, the study followed the ethical standards of the Declaration of Helsinki and Good Clinical Practice (ICH-GCP) guidelines. Approval was obtained from the Institutional Ethics Committee (IEC), and written informed consent was obtained from all participants.

A minimum sample size of 132 participants (66 per group) was determined based on a previous randomized control trial (RCT) by Zollinger et al. Between January 2023 and March 2023, 150 patients over 50 years old with unilateral distal radius fractures, treated either conservatively or surgically, were enrolled. After providing informed consent, participants were randomized into either the test group or the standard group. The test group received vitamin C (500 mg/day) plus standard therapy from the day of fracture management, while the standard group received only standard therapy for three months. Standard treatment included daily calcium (500 mg) and vitamin D (1000 IU) supplementation along with standard physiotherapy care. Randomization was performed using a computer-generated list with a 1:1 allocation using 4-block randomization.

**Inclusion Criteria**
- Patients over 50 years old
- Unilateral distal radius fractures
- Treated conservatively or surgically
- Able to provide written informed consent

**Exclusion Criteria**
- Patients under 50 years old
- Existing wrist deformity or wrist disease
- Previous distal radial fracture or bone surgery in the currently fractured distal forearm
- Taking vitamin C or multivitamin therapy prior to the fracture
- Renal impairment
- Muscular disorders
- Unable to provide consent

At enrolment, patient data such as age, gender, fracture side, type of fracture, and management details were recorded. Both groups were evaluated during routine visits for treatment compliance and CRPS features, based on continuing pain disproportionate to the inciting event and the Budapest criteria. An independent assessor diagnosed CRPS-1 among participants showing CRPS features. Upon diagnosis of CRPS-1, the study endpoint was reached, and participants were allowed to proceed with further CRPS treatment.

**Study Evaluation and Outcomes**

**CRPS-1 Occurrence:** The primary endpoint was the occurrence of CRPS-1, assessed using the Budapest clinical criteria within three months following fracture management. The Budapest criteria is a validated scale, known for its high specificity and maintained sensitivity in diagnosing CRPS. According to these criteria, a diagnosis of CRPS requires the presence of characteristics in at least three out of four symptom categories and at least two out of four sign categories.

**Time to CRPS-1 Diagnosis:** The average time between fracture management and the diagnosis of CRPS-1 was calculated.

**Probability of CRPS-1:** The Kaplan-Meier method was used to estimate the cumulative probability of developing CRPS-1, with the occurrence of CRPS-1 serving as the endpoint for both groups.

**Results:**
Out of 150 participants initially enrolled, six were excluded due to lack of follow-up or undergoing additional management or surgical procedures. The final analysis included 144 participants, with 71 receiving vitamin C along with standard treatment and 73 receiving only standard treatment.

**General Characteristics:**
Table 2 summarizes the general characteristics of participants in both groups. Most participants had distal radius fractures in the right wrist. The average age of participants in the vitamin C plus standard group was 56.5 ± 5.3 years, compared to 57.6 ± 8.5 years in the standard group. No significant differences in general characteristics were observed between the groups.

**CRPS-1 Occurrence:**
The overall prevalence of CRPS-1 in the study cohort was 18.8% (27 out of 144 participants). CRPS-1 occurred in 11.3% of participants in the vitamin C plus standard group (8 of 71) and 26% in the standard group (19 of 73). A significant difference was noted between the two groups (p = 0.023), with the relative risk of CRPS-1 being 0.43 (95% CI: 0.20–0.92) in the vitamin C group.

**Logistic Regression Analysis:**
Logistic regression was used to evaluate the impact of factors such as gender, smoking, alcohol use, comorbidities, fracture classification, and vitamin C therapy on CRPS-1 risk. Vitamin C therapy (500 mg) showed a significant odds ratio of 3.01 (95% CI: 1.12–8.13, p = 0.029), indicating a reduced likelihood of CRPS-1. Factors such as gender, smoking, alcohol, and comorbidities were not predictive of CRPS-1, though fracture classification was significantly associated (p < 0.001).

**Time to Diagnosis of CRPS-1:**
CRPS-1 was diagnosed on average 66 ± 12 days post-fracture management. In the vitamin C plus standard group, the average diagnosis time was 70 days, while in the standard group, it was 64 days. This difference was not statistically significant (t = 1.094, p = 0.284).

**Probability of CRPS-1:**
Kaplan-Meier estimates showed a higher cumulative probability of not developing CRPS-1 in the vitamin C plus standard group (88.7%) compared to the standard group (74%), with a significant difference (p = 0.020).

**Discussion**
This study found that vitamin C (500 mg/day) supplementation over 90 days was linked to a reduced incidence of acute CRPS-1, indicating that vitamin C could be a promising prophylactic option for preventing CRPS-1 following distal end radius fractures in older adults.

CRPS-1 is a debilitating condition that severely impacts function and quality of life, with a notably high prevalence after distal radius fractures. Estimates of CRPS incidence following such fractures vary widely, ranging from 1% to 37%. This variation might stem from differences in diagnostic scales and the absence of a definitive diagnostic test. Managing CRPS-1 remains challenging due to the lack of a definitive treatment, making prevention particularly important. Previous clinical trials have suggested that vitamin C, due to its antioxidant properties, may help prevent CRPS-1 in distal radius fractures, though results have been inconsistent.

Our study demonstrated that vitamin C supplementation, when combined with standard treatment, significantly reduced the incidence of CRPS-1 compared to standard treatment alone (11.3% vs. 26%, p = 0.023). This finding aligns with previous research by Zollinger et al., who found that 500 mg of vitamin C daily for 50 days reduced CRPS occurrence after wrist fractures. Zollinger et al. reported CRPS rates of 7% in the vitamin C group versus 22% in the placebo group in 1999, and 2.4% versus 10.1% in 2007, with significant differences (p = 0.002). Similarly, Cazeneuve et al. found lower CRPS prevalence with 1 gram of vitamin C daily for 45 days compared to controls.

The American Academy of Orthopaedic Surgeons' 2010 Clinical Practice Guideline supports vitamin C supplementation for preventing CRPS following distal radius fractures, which corroborates our findings. Despite this, a recent trial by Ekrol et al. presented conflicting results, showing no significant reduction in CRPS prevalence with vitamin C and even a higher CRPS rate in the vitamin C group for non-displaced fractures at 6 weeks (p = 0.022). This inconsistency is reflected in various meta-analyses on vitamin C's effectiveness in preventing CRPS, with some studies reporting no significant effect across different dosages, while others found a significant reduction with 500 mg daily.
Our study showed an overall CRPS-1 prevalence of 18.8%, lower than some population-based studies, likely due to our use of a validated clinician-based assessment scale rather than a patient-reported scale. The average time to diagnose CRPS-1 was 66 days in our study, consistent with Zollinger et al.'s 76 days. However, our findings showed an earlier diagnosis in the standard group compared to the vitamin C group, which contrasts with Zollinger et al.'s results where vitamin C led to earlier diagnoses.

The Kaplan-Meier estimate indicated a higher cumulative probability of not developing CRPS-1 in the vitamin C plus standard group (88.7%) compared to the standard group (74%, p = 0.020), echoing results from Zollinger et al.’s study. Overall, our study suggests that daily vitamin C supplementation for 90 days alongside standard treatment is associated with a reduced risk of CRPS-1 in distal radius fractures. Further large-scale randomized controlled trials are needed to confirm these results and support broader recommendations.

This study utilized the Budapest diagnostic criteria, which offers higher specificity and good sensitivity for diagnosing CRPS compared to other criteria that may rely on self-reported symptoms and miss motor and trophic features.

Conclusions:

In summary, our findings indicate that daily supplementation of vitamin C (500 mg) is linked to a reduced incidence of acute CRPS-1 following a distal end radius fracture. This suggests that vitamin C could be an effective preventive measure against CRPS-1. Nonetheless, additional well-designed randomized controlled trials with larger sample sizes are needed to confirm these results and to support broader recommendations.

References

