

# Testing the Validity of Preventing Complex Regional Pain Syndrome With Vitamin C After Distal Radius Fracture

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**Purpose** The American Academy of Orthopaedic Surgeons recommends the use of vitamin C to prevent complex regional pain syndrome (CRPS) for patients with distal radius fractures (DRFs). We hypothesized that the evidence for supporting this recommendation is weak, based on epidemiological principles of association and causality. The specific aim of this project was to test the validity of this recommendation.

**Methods** We conducted a literature review to retrieve articles reporting on the use of vitamin C to prevent CRPS. Data collected included sample size, study design type, dose of vitamin C used, and outcome measures of association expressed as relative risk (RR) and odds ratio. We then applied Hill criteria to evaluate the relationship between vitamin C and CRPS.

**Results** We obtained 225 articles from the database search. After the exclusion of duplicates, unrelated articles, editorial letters, and commentaries, we found 4 articles and 1 systematic review relevant to our topic. Six of the 9 Hill criteria were met, and an earlier meta-analysis showed a quantified reduction in CRPS risk. However, criteria like biological plausibility, specificity, and coherence were not met.

**Conclusions** The number of causal/association criteria met was adequate to support the scientific premise of the effect of vitamin C in preventing CRPS after DRF. Furthermore, vitamin C administration is of relatively low cost and has few complications unless administered in large doses. Owing to sufficient epidemiological evidence availability, the American Academy of Orthopaedic Surgeons recommendation of vitamin C to prevent CRPS has practical merit. (*J Hand Surg Am.* 2014;39(11):2251–2257. Copyright © 2014 by the American Society for Surgery of the Hand. All rights reserved.)

**Type of study/level of evidence** Therapeutic II.

**Key words** Bradford Hill criteria, CRPS, distal radius, prophylactic, vitamin C.

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**D**ISTAL RADIUS FRACTURES (DRFS) are common injuries in 2 groups of Americans.<sup>1</sup> Young adults experience complex fractures after high-impact trauma and elderly individuals sustain fractures after a fall owing to their fragile bones. Neurovascular, bone, and soft tissue complications can follow DRF.<sup>2</sup> Among the neurovascular complications, complex regional pain syndrome (CRPS) is of special concern because of its chronic and disabling nature. The reported incidence of CRPS varies greatly from 1% to 37% after DRFs<sup>3–5</sup> and 3% to 10% in patients with volar locking plate fixation after DRFs.<sup>2,6,7</sup> Use of vitamin C as a therapy to prevent the onset of CRPS in patients with DRFs is a topic of considerable debate.<sup>8–10</sup>

The American Academy of Orthopedic Surgeons (AAOS) develops evidence-based clinical practice guidelines to help surgeons better treat patients. These guidelines counsel surgeons on the treatment options, management of accompanying injuries, postoperative therapy, and complications. In a 2009 clinical practice guideline, the AAOS<sup>11</sup> recommended 500 mg of vitamin C every day for 50 days after DRF to prevent occurrence of CRPS. The strength of this recommendation was categorized as “moderate,” which means the evidence for such a recommendation was gathered from level II or level III studies with consistent findings or a single level I study in favor or against the intervention.<sup>11</sup> In other words, it means that the “benefits exceed the potential harm and that practitioners can follow the recommendation but remain alert to new information and be sensitive to patient preferences.”<sup>11</sup>

Vitamin C is readily accessible, relatively inexpensive, and does not have any substantial harmful effects. No matter how innocuous, owing to the lack of strong recommendation, such an arbitrary use may not be advantageous to prevent CRPS. Therefore, it is imperative to evaluate if any relationship exists between vitamin C and CRPS prevention. With an estimated prevalence rate of 21/100,000 and substantial work absences, CRPS poses a considerable financial impact on the health care system.<sup>12,13</sup> The aim of this paper was to critically examine the available studies to evaluate the AAOS recommendation based on epidemiological principles. We hypothesized that there was not enough scientific evidence to warrant the prophylactic use of vitamin C against CRPS.

## METHODS

### Literature search

The authors searched MEDLINE, EMBASE, and SCOPUS databases for relevant articles using the keywords “vitamin C” or “ascorbic acid” and “complex regional pain syndrome” or “reflex sympathetic dystrophy.” An experienced MPH researcher (S.M.) performed the search, with support from the university medical librarians. Affected condition was not limited to DRF alone, but included other conditions for which vitamin C was used to prevent CRPS development. We did not use any limit on the language of articles.

### Hill criteria

In 1965, Hill,<sup>14</sup> an epidemiologist, outlined the minimal conditions required to establish a causal relationship between an exposure and its effect. We applied these criteria to determine the relationship

between vitamin C and CRPS similar to health research in other medical specialties.<sup>15–17</sup> Strength of association, consistency, specificity, temporality, biological gradient (dose response relationship), biological plausibility, coherence, experimental evidence, and analogy constitute the 9 Hill criteria.<sup>14</sup> We determined a criterion to be met when a definition and explanation of it provided by Hill were valid with vitamin C and CRPS based on the available evidence. We did not find any information about the number of criteria to be met for an association to be considered causal, but we observed that, if majority of criteria were met, the authors considered the association to be causal.<sup>15–17</sup> In addition, there was a lack of information about the weightage of individual criteria. In the preparation of this manuscript, the authors adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.<sup>18</sup>

## RESULTS

### Literature search

We obtained 225 articles from 3 databases searched. We performed title and abstract search after the exclusion of duplicates. We excluded all unrelated articles, editorial letters, and commentaries. Four studies and 1 systematic review related to the use of vitamin C and CRPS were available for final review. Among the 4 studies, 3 were conducted in DRF patients and 1 was conducted in patients undergoing foot and ankle surgery.<sup>8,19–21</sup> We included the foot and ankle surgery article to add to the sample size for our analysis. The systematic review comprised the 4 original studies.<sup>22</sup> The type of study design, dose of vitamin C used, sample size, and CRPS outcome expressed as measures of association (relative risk [RR] and odds ratios [OR]) in these studies are presented in [Table 1](#).

### Hill criteria

**Strength of association:** The stronger association between the 2 variables indicates an increased likelihood of them being in a causal relationship as identified by the measures of association (OR, RR). The criterion strength of association is met for vitamin C and CRPS. Included studies in our review are summarized later. Zollinger et al<sup>19</sup> found that conservatively treated DRF patients randomized to vitamin C group (500 mg/d), and placebo group developed CRPS in 7% and 22%, respectively. An RR of 0.34 and an OR of 0.29 were observed in group treated with vitamin C compared with the group with placebo.

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