Objective: To determine whether vitamin C is effective in preventing complex regional pain syndrome (CRPS) in patients with distal radius fractures.

Data Sources: MEDLINE (1946 to present), EMBASE (1974 to present), and The Cochrane Library (no date limit) were systematically searched up to September 6, 2014, using MeSH and EMTREE headings with free text combinations.

Study Selection: Randomized trials comparing vitamin C against placebo were included. No exclusions were made during the selection of eligible trials on the basis of patient age, sex, fracture severity, or fracture treatment.

Data Extraction: Two reviewers independently screened articles, extracted data, and applied the Cochrane Risk of Bias tool. Evidence was graded using the Grading of Recommendations Assessment, Development, and Evaluation approach.

Data Synthesis: Heterogeneity was quantified using the $\chi^2$ test and the $I^2$ statistic. Outcome data were combined with a random effects model.

Results: Across 3 trials ($n = 890$) of patients with distal radius fractures, vitamin C did not reduce the risk for CRPS (risk ratio $= 0.45$; 95% confidence interval, 0.18–1.13; $I^2 = 70$%). This result was confirmed in sensitivity analyses to test the importance of missing data because of losses to follow-up under varying assumptions. Heterogeneity was explained by diagnostic criteria, but not regimen of vitamin C or fracture treatment.

Conclusions: The evidence for vitamin C to prevent CRPS in patients with distal radius fractures fails to demonstrate a significant benefit. The overall quality of the evidence is low, and these results should be interpreted in the context of clinical expertise and patient preferences.

Key Words: vitamin C, distal radius, CRPS, complex regional pain syndrome, meta-analysis, systematic review, randomized controlled trials

INTRODUCTION

Complex regional pain syndrome (CRPS) is a debilitating condition that affects as many as 10% of all patients with distal radius fractures. CRPS is characterized by dysfunction of the autonomic nervous system, and patients with CRPS experience neuropathic pain, vasomotor instability, abnormal sweating and swelling, and joint and soft tissue stiffness. CRPS has been previously referred to as causalgia, reflex sympathetic dystrophy, and algodystrophy.

Several sets of diagnostic criteria have been proposed for CRPS, but the current literature remains controversial, and there is no agreed upon reference standard. Veldman et al. suggested a system based on the presence of 4 or 5 specific signs and symptoms, and Atkins et al. required 3 or more. The Budapest criteria require continuing pain disproportionate to the inciting event, symptoms in at least 3 of 4 sensory, vasomotor, sudomotor/edema, and motor/trophic categories, 2 or more signs at the time of evaluation, and absence of a plausible alternative diagnosis.

Vitamin C has been suggested as a low-risk intervention that might limit excessive soft tissue injury and prevent CRPS. Vitamin C is thought to act by inhibiting local pro-inflammatory cascades via antioxidant mechanisms. No adverse effects attributable to its use have been reported in patients with fractures, and animal studies suggest that it may even accelerate fracture healing.

Two early randomized controlled trials reported consistent efficacy, and the 2010 American Academy of Orthopaedic Surgeons (AAOS) Clinical Practice Guideline included a moderate strength recommendation that the treatment of distal radius fractures should include adjuvant vitamin C for the prevention of disproportionate pain. However, a more recently published trial reported a conflicting result, and an updated meta-analysis is required to understand differences between studies, detect bias, and direct future research.
The primary objective of this systematic review and meta-analysis was to determine whether vitamin C is effective in preventing CRPS in patients with distal radius fractures within 1 year of follow-up, based on evidence from randomized controlled trials. Additional objectives were to explore reasons for heterogeneity between trials and evaluate the overall quality of the current evidence.12

METHODS

This study was conducted according to the Cochrane Handbook and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.13,14

Eligibility Criteria

All randomized controlled trials that compared vitamin C against placebo in patients with distal radius fractures were included. Observational studies were excluded to focus on research with the lowest risk of bias.15 No exclusions were made during the selection of eligible trials on the basis of patient age, sex, fracture severity, fracture treatment, regimen of vitamin C, date of publication, language, or publication status.

Identification of Studies

MEDLINE (1946 to present), EMBASE (1974 to present), and The Cochrane Library (no date limit) were systematically searched up to September 6, 2014. MeSH and EMTREE headings and subheadings were used in various combinations, supplemented with free text [ie, [Ascorbic Acid.mp. or Ascorbic Acid/] OR [Vitamin C.mp]] AND [[wrist.mp. or Wrist/or Wrist Injuries/] OR (Radius Fractures/ or Radius/or radius.mp)]. Hand searching the reference lists of the included trials, consultations with experts, and the “related articles” feature in PubMed were used to search for additional articles. Conference proceedings from the AAOS and the OTA meetings for last 3 years and the database of http://www.clinicaltrials.gov/ were also searched for unpublished studies.

Assessments of Eligibility

Two reviewers independently screened all titles and abstracts for eligibility. All discrepancies were resolved by consensus.

Data Collection

The 2 reviewers independently graded the risk of bias of each study using the Cochrane Collaboration’s Risk of Bias tool.13 The 2 reviewers independently extracted study data using piloted data forms. Data points included the following: author, journal, year of publication, funding, age, sex, fracture characteristics, operative and/or nonoperative management, definition of CRPS, vitamin C regimen, number of patients randomized to each arm, and number of patients followed up in each arm.

Outcomes were classified as critical, important but not critical, or of limited importance.16 Incidence of CRPS and potential complications were considered critical, and patient-reported function was considered important. Range of motion, grip strength, pain, radiographic parameters, and complaints in plaster were considered to be of limited importance and were not pooled. Attempts were made to pool data separately at early and 1 year of follow-up.

Statistical Analyses

Interobserver agreement for the reviewers’ assessments of study eligibility was calculated with Cohen kappa (IBM SPSS Version 21; IMB Corp, Armonk, NY; 2012).17,18 Outcome data were combined according to the inverse variance method using a random effects model.13 The primary meta-analysis was an intention-to-treat analysis in which all patients were analyzed in the groups to which they were originally randomized. Patients with missing data were assumed to be free of CRPS, but this assumption was tested with sensitivity analyses in which (1) all patients with missing data were assumed to have CRPS and (2) all patients with missing data were excluded from the analysis.

Pooled estimates are reported as risk ratios (RR) with 95% confidence intervals (CIs). RR were converted to number needed to treat to provide benefit (NNT) to aid interpretability.19 Continuous outcomes are reported as mean differences with 95% CIs. A minimal important difference (MID) of 10.2 points on the Disabilities of the Arm, Shoulder, and Hand (DASH) scale was considered clinically significant.20

Heterogeneity was quantified using the $\chi^2$ statistic for heterogeneity and the $I^2$ statistic. A priori subgroup hypotheses to explain high heterogeneity included the enrolment of patients with varying ages or sex, the inclusion of patients with operative versus nonoperative management, varying regimens of vitamin C, and varying diagnostic criteria for CRPS.21

For trials with statistically significant dichotomous primary outcomes, the fragility index describes the minimum number of patients whose status would have to change from a nonevent to an event to turn a statistically significant result to a nonsignificant result.22 A sensitivity analysis to explore overall fragility was performed by varying the event rates in either arm of studies with statistically significant results by the fragility index for that study.

All tests of significance were 2 tailed, and $P$ values of less than 0.05 were considered significant. A funnel plot was planned to detect publication bias but was omitted because of lack of interpretability given the small number of included studies.13 The forest plots were created with Review Manager 5.2 (The Nordic Cochrane Center, The Cochrane Collaboration, 2012, Copenhagen, Denmark).

Grades of Recommendation, Assessment, Development, and Evaluation Quality Assessment and Summary of Findings

The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group has developed a system for grading the quality of evidence that has been adopted by over 70 major health research organizations.12,13,23 Data from randomized controlled trials were considered high-quality evidence but could be rated down according to risk of bias, imprecision, inconsistency, indirectness, or publication bias. The evidence was graded by 2 independent assessors, and discrepancies were resolved by consensus.

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RESULTS

Included Studies

There were 127 articles identified by the search strategy, and 3 trials were included in the final meta-analysis (n = 890 fractures) (Fig. 1). Agreement between the reviewers for screening of titles and abstracts was satisfactory (kappa = 0.70). The disagreements resulted because one of the reviewers included commentaries and duplicate publications that the other reviewer excluded.

All 3 trials included predominantly older females and a mix of intra- and extra-articular fractures (Table 1). In 2 trials, patients were treated with operative and nonoperative techniques, whereas 1 trial included only nonoperative management. Two trials randomized patients to 500 mg of vitamin C daily for 50 days versus placebo (1:1), whereas 1 randomized patients to 200, 500, or 1500 mg of vitamin C daily for 50 days versus placebo (3:1). CRPS was diagnosed according to the criteria of Veldman in 2 studies and according to the criteria of Atkins in the third. Two of the studies had statistically significant dichotomous primary outcomes, and their fragility indices were each one event or fewer.

Risk of Bias

All 3 trials were determined to be at low risk of bias (see Figure, Supplemental Digital Content 1, http://links.lww.com/BOT/A302) for each category of randomization, allocation concealment, blinding, and reporting of losses to follow-up. Only one trial reported on potential harms, raising the possibility of selective outcome reporting in the other two.

Incidence of CRPS

All 3 trials reported on incidence of CRPS at 1 year (n = 890). The pooled RR for CRPS with vitamin C in comparison with placebo was 0.45 (95% CI, 0.18–1.13; NNT = 14; 95% CI NNT, 9 to no benefit; heterogeneity P = 0.04; I² = 70%; Fig. 2A). This result was robust to sensitivity testing in which all patients with missing data were assumed to have CRPS (Fig. 2B) or all patients with missing data were excluded from the analysis (Fig. 2C). The RR of CRPS at 6 weeks according to one trial was 1.24 with vitamin C (95% CI, 0.90–1.69). Varying the event rates by the fragility index in either arm of the 2 studies with statistically significant individual study results did not produce a statistically significant pooled result.

Heterogeneity was not resolved by the exclusion of patients who received doses of vitamin C other than 500 mg daily (RR = 0.44; 95% CI, 0.16–1.24; heterogeneity P = 0.06; I² = 65%) or by the exclusion of trials that only managed patients nonoperatively (RR = 0.50; 95% CI, 0.13–2.00; heterogeneity P = 0.02; I² = 83%). However, heterogeneity was resolved when the trials were pooled in subgroups according to how CRPS was diagnosed (Table 2). Across the 2 trials that diagnosed CRPS according to the criteria of Atkins et al., the pooled RR was 0.28 (95% CI, 0.14–0.55; NNT = 11; 95% CI, 9–17; heterogeneity P = 0.66; I² = 0%). The RR in the single trial that diagnosed CRPS according to the criteria of Atkins et al. was 0.99 (95% CI, 0.49–2.01; heterogeneity, not available).

Function and Complications

One trial evaluated patient-reported function using the DASH scale (n = 336). The mean difference between groups was not statistically significant and did not exceed the MID (mean difference = 1.30 in favor of placebo, 95% CI, −2.12 to 4.72; MID = 10.2 points). Complications were reported in the same trial as a composite that included loss of reduction, paresthesias, superficial infections in surgically treated patients, and tendon injuries. This composite was not statistically significant (RR = 1.57 with vitamin C, 95% CI, 0.89–2.77; number needed to treat to cause harm = 15, 95% CI, 45 to no harm), and the individual components were not reported separately.

GRADE Assessment

Table 3 presents the reviewers’ assessments of the overall quality of the evidence according to the GRADE approach. Both reviewers rated down the quality of the evidence for the outcome incidence of CRPS, function (DASH), and complications to “low” based on imprecision and inconsistency. The imprecision was because of wide CIs that crossed the line of no effect with limited total sample size, whereas the inconsistency was because of the high unexplained residual heterogeneity and lack of additional comparable trials (Table 3). Table 3 also contains estimates of anticipated absolute effect sizes for each outcome, expressed as NNT with 95% CIs. The estimated pooled NNT with vitamin C to prevent one case of CRPS in comparison with placebo was 14, but the 95% CI spanned from 9 patients to no benefit.

DISCUSSION

The literature is conflicting and fails to demonstrate a statistically significant effect for vitamin C in preventing CRPS in patients with distal radius fractures. Heterogeneity in
the pooled estimate was explained according to the diagnostic criteria that the trials employed. Across 2 trials that used the criteria of Veldman et al, the number of patients needed to treat with vitamin C to prevent CRPS in 1 patient was 11 (95% CI, 9–17), whereas the single trial that used the criteria of Atkins et al found no benefit.

### Implications for Research

In 1993, Veldman et al proposed diagnostic criteria for reflex sympathetic dystrophy based on a series of 829 consecutive patients. The criteria included 4 or 5 out of unexplained diffuse pain, a difference in skin color, a difference in skin temperature, diffuse swelling, or limited active range of motion; occurrence or increase in signs and symptoms after use; and presence of these signs and symptoms in an area larger than the area of injury or operation and including the area distal to the primary injury. In contrast, Atkins et al proposed diagnosis based on just 3 or more of neuropathic pain, vasomotor instability, abnormalities of sweating and swelling, loss of joint mobility, and joint and soft tissue contractures.

The criteria of Atkins et al appear to require fewer clinical features and may have greater sensitivity than the criteria of Veldman et al, but there is no gold standard test for CRPS, and the 2 systems have never been compared directly. Differences in the diagnostic criteria appeared to resolve the heterogeneity seen in the primary analysis, which suggests that further research accounting for this apparent subgroup effect is warranted. Harden et al reported validation of an alternative system, the “Budapest criteria,” which was subsequently accepted by the Committee for Classification of Chronic Pain of the International Association for the Study of Pain. Nonetheless, the current literature remains

### Table 1. Randomized Controlled Trials of Vitamin C Versus Placebo to Prevent CRPS in Patients With Distal Radius Fractures That Were Included in the Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Funding</th>
<th>Sample Size</th>
<th>Mean Age</th>
<th>% Males</th>
<th>% Operative</th>
<th>% Extra-articular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zollinger et al</td>
<td>1999</td>
<td>The Netherlands</td>
<td>Not reported</td>
<td>127</td>
<td>58.6</td>
<td>21.0</td>
<td>0.0</td>
<td>63.0</td>
</tr>
<tr>
<td>Zollinger et al</td>
<td>2007</td>
<td>The Netherlands</td>
<td>Other*</td>
<td>427</td>
<td>62.4</td>
<td>17.7</td>
<td>11.0</td>
<td>54.5</td>
</tr>
<tr>
<td>Ekrol et al</td>
<td>2014</td>
<td>United Kingdom</td>
<td>Government</td>
<td>336</td>
<td>56.6</td>
<td>26.8</td>
<td>25.0</td>
<td>47.9</td>
</tr>
</tbody>
</table>

*The authors of this study disclosed that “in support of their research for or preparation of this work, one or more of the authors received, in any 1 year, outside funding or grants in excess of $10,000 from Stichting Achmea Slachtoffer en Samenleving (SASS).” Achmea is an insurance company in The Netherlands, and SASS is the foundation from Achmea that financially supports research.

### Figure 2.

Forest plot showing pooled RR for CRPS with vitamin C in comparison with placebo: (A) primary intention-to-treat analysis, (B) sensitivity analysis in which all patients with missing data were assumed to have CRPS, and (C) sensitivity analysis in which all patients with missing data were excluded from the analysis.
Management: include only those trials in which all patients were managed nonoperatively; randomized trials 259 (1 study) 1 y

Outcomes

<table>
<thead>
<tr>
<th>Subgroup Hypothesis</th>
<th>No. Studies</th>
<th>Pooled RR; 95% CI</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin C regimen: 500 mg daily only</td>
<td>2</td>
<td>0.44; 0.16–1.24</td>
<td>P = 0.06, I² = 65%</td>
</tr>
<tr>
<td>Management: exclude those trials in which all patients were managed nonoperatively</td>
<td>2</td>
<td>0.50; 0.13–2.00</td>
<td>P = 0.02, I² = 83%</td>
</tr>
<tr>
<td>Management: include only those trials in which all patients were managed nonoperatively</td>
<td>1</td>
<td>0.33; 0.11–0.95</td>
<td>NA</td>
</tr>
<tr>
<td>Diagnosis: CRPS as per Veldman et al†</td>
<td>2</td>
<td>0.28; 0.14–0.55</td>
<td>P = 0.66, I² = 0%</td>
</tr>
<tr>
<td>Diagnosis: CRPS as per Atkins et al†</td>
<td>1</td>
<td>0.99; 0.49–2.01</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA, not available.

controversial, and future studies should clearly describe their choice of diagnostic criteria.

All 3 studies included patients with similar age and sex distributions; the percentage of operative patients ranged from 0 to 25; and approximately half of the fractures were extra-articular as diagnosed by radiographs. Suggested risk factors that increase the likelihood of developing CRPS include female sex, older age, and medium- to low-energy trauma.24,27 In a subgroup analysis of one of the included trials, the use of external fixation was not associated with increased rates of CRPS.28 Further research is necessary to understand whether certain patient, injury, or treatment factors might increase the risk for CRPS and whether vitamin C might specifically be useful in these populations.29 Future studies should also be adequately powered to examine varying populations in subgroup analyses.

Implications for Practice

In a survey of members of the American Society for Surgery of the Hand, only 11% of 469 respondents reported routinely prescribing vitamin C for patients with distal radius fractures while 49% reported never doing so.30 The reasons for these preferences remain unclear but seem to contradict the moderate strength recommendation of the AAOS guidelines.9 The overall quality of the evidence in this meta-analysis was low, which is compatible with a variety of treatment decisions based on clinical expertise and patient preferences. Vitamin C dosed at 500 mg daily for 50 days does not seem to be associated with any harm.

The results in this meta-analysis contradict an earlier meta-analysis, but several potential factors account for the difference.31 The earlier study was published before the latest trial was available, included foot and ankle injuries, and included observational studies alongside randomized trials.32,33 Observational studies are at risk of systematically overestimating apparent treatment effects.34 The randomized controlled trials included in this meta-analysis were at low risk of bias, but the small fragility indices indicate a lack of the robustness associated with very large sample sizes.32

Limitations

There were 85 losses across the 3 trials. Sensitivity testing for missing data did not substantially alter the pooled

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TABLE 3. GRADE Summary of Findings

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. Participants (Studies) Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Anticipated Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of CRPS, randomized trials</td>
<td>890 (3 studies) 1 y</td>
<td>☒ ☒ ☒; Low because of imprecision, inconsistency</td>
<td>The RR for CRPS with vitamin C in comparison with placebo is 0.45 (95% CI, 0.18–1.13). This is equivalent to an estimated NNT of 14 (95% CI NNT, 9 to no benefit)*</td>
</tr>
<tr>
<td>Function (DASH); randomized trials</td>
<td>259 (1 study) 1 y</td>
<td>☒ ☒ ☒; Low because of imprecision, inconsistency</td>
<td>The mean difference in DASH scores was 1.30 (95% CI, −2.60 to 5.20) in favor of placebo, which was not clinically or statistically significant</td>
</tr>
<tr>
<td>Complications; randomized trials</td>
<td>259 (1 study) 1 y</td>
<td>☒ ☒ ☒; Low because of imprecision, inconsistency</td>
<td>The RR for complications with vitamin C in comparison with placebo is 1.48 (95% CI, 0.85–2.58). This is equivalent to an estimated NNH of 15 (95% CI NNH, 49 to no harm)†</td>
</tr>
</tbody>
</table>

GRADE Working Group grades of evidence. High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.

*Calculation assumes a baseline control event rate of 12.6% based on the weighted pooled event rate from the placebo arms of each trial.
†Calculation assumes a baseline control event rate of 13.6% based on the event rate from the placebo arms of the included trial.

NNH, number needed to treat to cause harm; NNT, number needed to treat to provide benefit.
estimates, but the handling of missing data in clinical research is often problematic. The scenario in which all missing patients were assumed to have CRPS is improbable because patients with CRPS could reasonably be expected to seek further care, but it was included to contrast with the primary analysis in which all these patients were assumed to not have CRPS.

The inclusion of observational studies could have increased the statistical power of this meta-analysis, but it would have also reduced the quality of the evidence and resulted in substantial uncertainty. According to the GRADE approach, data from observational studies are considered low quality and can only be graded up in the setting of large treatment effects or evidence of a dose–response relationship. We identified only one observational study that compared the use of vitamin C against placebo or no treatment in patients with distal radius fractures, and it did not have a large treatment effect or evidence of a dose–response relationship. Furthermore, it also did report which set of diagnostic criteria was used to diagnose CRPS and cannot be used to clarify which set of diagnostic criteria is optimal.

Although all trials evaluated outcomes at 1 year of follow-up, only one trial included results within the first 6 weeks. In the series of Veldman et al of 829 patients with reflex sympathetic dystrophy, 75% experienced symptom onset within 1 day of the inciting trauma or other precipitant but only 28% reported that their symptoms lasted for more than 12 months. It is possible that an important subgroup of patients experienced CRPS at less than 1 year of follow-up, but their symptoms resolved before 1-year outcomes were assessed and their events missed. Further research is necessary to investigate whether vitamin C might be effective at shortening the duration of symptoms in those patients who develop CRPS in addition to clarifying its role in prevention. Likewise, only one study reported on functional outcomes and rates of complications, and future studies should evaluate and report all patient-important outcomes to avoid this limitation.

CONCLUSIONS

The evidence for vitamin C to prevent CRPS in patients with distal radius fractures is conflicting and fails to demonstrate a statistically significant effect. The overall quality of the evidence was low, and these results should be interpreted in the context of clinical expertise and patient preferences. According to the GRADE approach, further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate itself.

REFERENCES


