Efficacy and Safety of High-dose Vitamin C on Complex Regional Pain Syndrome in Extremity Trauma and Surgery—Systematic Review and Meta-Analysis

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A R T I C L E  I N F O

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- chronic pain
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A B S T R A C T

Complex regional pain syndrome (CRPS) is a devastating condition often seen after foot and ankle injury and surgery. Prevention of this pathology is attractive not only to patients but also to surgeons, because the treatment of this condition can be difficult. We evaluated the effectiveness of vitamin C in preventing occurrence of CRPS in extremity trauma and surgery by systematically reviewing relevant studies. The databases used for this review included: Ovid EMBASE, Ovid MEDLINE, CINAHL, and the Cochrane Database. We searched for comparative studies that evaluated the efficacy of more than 500 mg of daily vitamin C. After screening for inclusion and exclusion criteria, we identified 4 studies that were relevant to our study question. Only 1 of these 4 studies was on foot and ankle surgery; the rest concerned the upper extremities. All 4 studies were in favor of this intervention with minimal heterogeneity (Tau^2 = 0.00). Our quantitative synthesis showed a relative risk of 0.22 (95% confidence interval = 0.12, 0.39) when daily vitamin C of at least 500 mg was initiated immediately after the extremity surgery or injury and continued for 45 to 50 days. A routine, daily administration of vitamin C may be beneficial in foot and ankle surgery or injury to avoid CRPS. Further foot and ankle specific and dose-response studies are warranted.

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Complex regional pain syndrome (CRPS) is a devastating condition, common after foot and ankle injuries and surgeries (1). CRPS causes diffuse pain in the extremities that is not isolated to the area of injury or surgery. The condition usually initiates from some form of traumatic stimuli, including injury and surgical intervention (2,3). Patients with this condition often complain of edema, erythema, sudomotor, and motor dysfunctions (2,4,5). Prognosis of this condition is fair when treated early, but becomes poor when it becomes chronic (1,6–8). It has been shown that a high percentage of this condition can involve lawsuits and worker’s compensation cases (9). Therefore, prevention of this condition is attractive not only to patients but also to surgeons. Use of high-dose vitamin C has been recommended by the Evidence Based Guidelines for Type 1 CRPS for a daily use of vitamin C of more than 500 mg, as recommended by the guidelines (10).

Although the exact mechanism by which vitamin C counteracts CRPS is unknown, the antioxidant property of ascorbate may be responsible for stabilizing free radicals that would normally damage lipid membranes or microcirculation (11–13). Treatment of CRPS with other free radical scavengers has also been studied (14). Vitamin C is a relatively safe supplement that is inexpensive and accessible to many; therefore, if effective, the intervention could be routinely used in foot and ankle trauma and surgeries to great benefit. Our objective in this study was to evaluate the effectiveness of this intervention in preventing occurrence of CRPS in trauma and surgery in the extremities by systematically reviewing and analyzing relevant clinical trials.

MATERIALS AND METHODS

Inclusion of studies was not limited to those regarding foot and ankle. Studies on surgically and traumatically induced CRPS in the upper extremities were also considered. Only peer-reviewed manuscripts were considered. Intervention of interest was a daily use of vitamin C of more than 500 mg, as recommended by the guidelines (10).
immobilized patients were included (331 total patients). They compared daily doses of 200, 500, or 1500 mg of vitamin C versus placebo. The intervention was carried out for 50 days, starting with the day of injury. For our study, those who received less than 500 mg of vitamin C in their study were not analyzed, in order to fulfill our exclusion criteria. Therefore, the group who received the 200-mg dose was not included in our analysis. In their study, CRPS was diagnosed with the clinical criteria described by Veldman et al (4). No patient was lost to follow-up. There was no reported complication from the high-dose vitamin C.

Besse et al investigated the effect of vitamin C in preventing CRPS after foot and ankle surgeries (11). They enrolled 420 patients via a “before-after” quasi-experimental study design. During the first year of the study, the patients did not receive vitamin C. All the participants who received vitamin C came from the second half of the study. The single surgeon who did all the surgeries was also an observer for the study. They used the International Association for the Study of Pain criteria (20) to diagnose CRPS. Their intervention was a daily dose of 1 g of vitamin C starting on the first postoperative day and continuing for 45 days. Their statistician was blinded to treatment group. There was no reported complication from the high-dose vitamin C in the study. One patient was dropped out of the study after discontinuing vitamin C after day 1. The reason for discontinuation was not stated.

Potential biases in these studies are summarized in Figure 3. Both studies from Zollinger et al were double-blind designs and the participants were randomized into either placebo or the vitamin therapy. The other 2 studies had a quasi-experimental design, or were retrospective, without randomization or blinding. A primary outcome measure for all 4 studies was the development of CRPS. There was no detectable reporting bias in any of these 4 studies. All 4 studies were in favor of prophylactic use of the high-dose vitamin C for prevention of CRPS. Overall, the RR calculated from this quantitative synthesis was 0.22 (95% CI = 0.12, 0.39), which was statistically significant (Fig. 2). Heterogeneity (Tau²) was 0.00.

### Discussion

High-dose vitamin C has been postulated to be beneficial for many conditions (21–32) and is relatively safe in healthy individuals

<table>
<thead>
<tr>
<th>Table 1</th>
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<tr>
<td>Terms used for an electronic search. At least one term from each group had to be in the search for a study to be retrieved</td>
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<tr>
<td>Group 1</td>
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<tr>
<td>1. Vitamin C</td>
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<tr>
<td>2. Ascorbic acid</td>
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<tr>
<td>3. Causalgia</td>
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<tr>
<td>4. Algodystrophy</td>
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<td>6. Sudek’s dystrophy</td>
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The outcome measures of interest were development of CRPS after a traumatic event and complications associated with the high-dose vitamin C, if any.

An electronic data search was conducted on August 1, 2012, using a keyword search strategy. Keywords used for this search are listed in Table 1. The databases used for this review included: Ovid EMBASE, Ovid MEDLINE, CINAHL, and the Cochrane Database. No language restriction was set. Google Translate (translate.google.com) was used for translation of foreign languages for screening purposes. All the authors were present in the same room to screen and discuss the articles. Each investigator initially screened the search results independently, and disagreements were discussed among the investigators until agreement was reached.

Inclusion and exclusion criteria are listed in Table 2. After the initial search, the titles were screened for exclusion. The second screening process was performed using the abstract. If an abstract was not available, the actual article was obtained and screened for inclusion and exclusion criteria in the next step. At this point, duplicate studies were eliminated. All the investigators read the remaining articles in their entirety for final selection. Characteristics of each study and potential biases were evaluated and presented using a risk of bias summary chart.

For each study under consideration, we abstracted the number of patients treated with or without vitamin C (or placebo), and for each group, those with CRPS and those without. Using RevMan 5 (Review Manager [RevMan; computer program], Version 5.1, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011), relative risks (RRs) and confidence intervals (CIs) were computed and pooled using the random effects Mantel-Haenszel method. Random effects were used to account for the variability in study populations: elective and emergent surgery, surgical and conservative therapy. The other 2 studies had a quasi-experimental design, or were retrospective, without randomization or blinding. A primary outcome measure for all 4 studies was the development of CRPS. There was no reported complication from the high-dose vitamin C.

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### Discussion

High-dose vitamin C has been postulated to be beneficial for many conditions (21–32) and is relatively safe in healthy individuals
(22,32–35). However, some adverse effects have been reported. Renal failure has been reported in patients who received a single intravenous high-dose of vitamin C of 2.5 to 45 g (36–38). Also, hemolysis in patients with known glucose-6-phosphate dehydrogenase deficiency has been reported (39,40). The patients in these case reports were receiving intravenous ascorbic acid of 40 to 80 g at a time. All of the patients who had these side effects had severe underlying health issues before the high-dose treatment. No study has been able to control for possible confounders that may be the actual causative factor for these complications. The most common complication from high-dose vitamin C reported from a survey conducted among complementary alternative medicine practitioners was fatigue and

Fig. 1. A study flow diagram.

Fig. 2. A forest plot showing RR of developing CRPS when high-dose vitamin C is administered daily for each of 4 studies. A cumulative RR is also presented. For each study the number of cases of CRPS (events) in each arm is shown as compared to all patients within the arm (total).
the vitamin C dosages in the studies that we reviewed in this article an average dose of 28 g every 4 days. It should be noted that lethargy (35). This was reported in 59 of 9328 patients who received each included study.

We feel that this finding is clinically significant: an approximately 5-fold reduction in occurrence of CRPS can be achieved with a daily 500-mg dose of vitamin C. Our meta-analysis also indicated a statistically significant reduction of CRPS in the group who received the high-dose vitamin C. We are not aware of any published data or ongoing projects. We are not aware of any ongoing projects, but we did not methodologically search for these potential data.

We felt that 2 of the 4 studies were at low risk for selection biases because they used a double-blind, randomized study design. It should be noted, however, that the primary authors for these 2 studies were the same. On the other hand, the other 2 studies had no randomization. Vitamin C was not administered in the ongoing projects, but we did not methodologically search for these potential data.

Based on our current review, vitamin C, when taken in a daily dose of more than 500 mg for 45 to 50 days post trauma or surgery, may help reduce the occurrence of CRPS after a traumatic event in the extremities. Because it is relatively inexpensive and safe, routine use of this supplement in foot and ankle surgery or injury may be beneficial. A foot and ankle-specific, double-blind, randomized clinical trial would be beneficial to solidify this recommendation.

References


