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 (Tau² = 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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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 (Taul2) 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 1 |
|-----------------|-----------------|
| 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 |
| Group 1 | Group 2 |
| 1. Vitamin C | 1. Complex regional pain syndrome |
| 2. Ascorbic acid | 2. Reflex sympathetic dystrophy |
| 3. Vitamin C | 3. Causalgia |
| 4. Participants having trauma or surgery | 4. Chronic pain |

* Truncation.
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
lethargy (35). This was reported in 59 of 9328 patients who received an average dose of 28 g every 4 days. It should be noted that vitamin C dosages in the studies that we reviewed in this article were signiﬁcant reductions of CRPS in the group who received the high-dose vitamin C. 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, started on the day of trauma. Because vitamin C is inexpensive and relatively safe, this regimen may be used in the practice routinely.

There are a few potential biases in our review process. First, the majority of studies were excluded via the title search. In this process, there may have been some valuable studies that were excluded from our final analysis. However, current guidelines and review articles, as well as the 4 included studies, did not mention any other relevant studies that we potentially missed. Second, we did not include any unpublished 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 same. On the other hand, the other 2 studies had no randomization. Vitamin C was not administered in the same projects, but we did not methodologically search for these potential data.

In the clinical setting, CRPS is diagnosed with one or more clinical diagnostic criteria. Many diagnostic tests are available (41–45), but clinical diagnosis is still the gold standard (46–50). Radiographic evaluation of the condition has also been examined in some cross-sectional studies, but it may not have an adequate sensitivity (46,51–53). Therefore, clinical diagnosis as well as research deﬁnitions of CRPS must rely greatly on subjective clinical ﬁndings. This may be the reason that many lawsuits and worker’s compensation cases involve this condition. Similarly, we ought to look at the studies involving CRPS with caution. Again, 2 out of 4 studies we reviewed had a double-blind design, which eliminates the possibility of favoring one group over the other.

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


