Can Vitamin C Prevent Complex Regional Pain Syndrome in Patients with Wrist Fractures?
A Randomized, Controlled, Multicenter Dose-Response Study

By P.E. Zollinger, MD, W.E. Tuinebreijer, MD, PhD, MSc, MA, R.S. Breederveld, MD, PhD, and R.W. Kreis, MD, PhD

Investigation performed at the Department of Surgery, Red Cross Hospital, Beverwijk, The Netherlands; the Department of Orthopaedics and Surgery, Haga Hospital (Leyenburg), The Hague, The Netherlands; and the Department of Orthopaedics and Surgery, Reinier de Graaf Group, Delft, The Netherlands

Background: Complex regional pain syndrome type I is treated symptomatically. A protective effect of vitamin C (ascorbic acid) has been reported previously. A dose-response study was designed to evaluate its effect in patients with wrist fractures.

Methods: In a double-blind, prospective, multicenter trial, 416 patients with 427 wrist fractures were randomly allocated to treatment with placebo or treatment with 200, 500, or 1500 mg of vitamin C daily for fifty days. The effect of gender, age, fracture type, and cast-related complaints on the occurrence of complex regional pain syndrome was analyzed.

Results: Three hundred and seventeen patients with 328 fractures were randomized to receive vitamin C, and ninety-nine patients with ninety-nine fractures were randomized to receive a placebo. The prevalence of complex regional pain syndrome was 2.4% (eight of 328) in the vitamin C group and 10.1% (ten of ninety-nine) in the placebo group (p = 0.002); all of the affected patients were elderly women. Analysis of the different doses of vitamin C showed that the prevalence of complex regional pain syndrome was 4.2% (four of ninety-six) in the 200-mg group (relative risk, 0.41; 95% confidence interval, 0.13 to 1.27), 1.8% (two of 114) in the 500-mg group (relative risk, 0.17; 95% confidence interval, 0.04 to 0.77), and 1.7% (two of 118) in the 1500-mg group (relative risk, 0.17; 95% confidence interval, 0.04 to 0.75). Early cast-related complaints predicted the development of complex regional pain syndrome (relative risk, 5.35; 95% confidence interval, 2.13 to 13.42).

Conclusions: Vitamin C reduces the prevalence of complex regional pain syndrome after wrist fractures. A daily dose of 500 mg for fifty days is recommended.

Level of Evidence: Therapeutic Level I. See Instructions to Authors for a complete description of levels of evidence.

Complex regional pain syndrome type I (formerly known as reflex sympathetic dystrophy) is treated symptomatically, and the clinical focus is on prevention. In patients who have sustained major trauma, the capacity of homeostasis can be overwhelmed, which can lead to systemic inflammatory response syndrome and multiple-organ distress syndrome. Systemic inflammatory response syndrome is an excessive inflammatory reaction to an event such as a trauma, burn, or massive infection (as in the case of pancreatitis). These processes appear to be mediated by the same host-derived inflammatory mediators. In an earlier report, we suggested a parallel between burn wounds and the development of complex regional pain syndrome because of the inflammatory reaction and the involved microangiopathy. Complex regional pain syndrome and burn wounds may involve a cascade of deterioration and exaggeration of a similar process.

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Tanaka et al. reported that, in the clinical setting, ascorbic acid given in high doses during the first twenty-four hours of burn resuscitation significantly reduces resuscitation fluid volume requirements and wound edema. The severity of respiratory dysfunction was also reduced in these patients. The increased vascular permeability in patients with burns is a result of damage to the microvascular endothelial cells caused by oxygen free radicals. Vitamin C reduces lipid peroxidation, scavenges hydroxyl radicals, protects the capillary endothelium, and inhibits vascular permeability. In a previous randomized trial, we reported that treatment with 500 mg of vitamin C, as compared with placebo, reduced the risk of reflex sympathetic dystrophy in patients with nonoperatively treated wrist fractures. Therefore, we performed a dose-response study to replicate and further evaluate our earlier findings. A steady state in human plasma at doses of >200 mg of ascorbic acid (vitamin C) per day has been reported. We performed a multicenter dose-response study of patients with all types of wrist fractures that were treated operatively and nonoperatively; the analysis was performed on the basis of the intention-to-treat principle.

Materials and Methods

Study Design

The trial was designed as a multicenter, randomized, controlled study. Three hospitals in The Netherlands participated in the study. The appropriate medical ethics committees of these three hospitals approved the study. An independent physician was appointed (as required under Dutch legislation) for the patients’ guidance in case they requested extra information about clinical trials in general or this trial in particular.

Adult patients (defined as those who were eighteen years of age or older) with a wrist fracture who were seen in the emergency department of each hospital were asked by the emergency department physician to participate in the study. Patients with a fracture of both wrists were also included. All wrist fractures were included, independent of treatment choice. Nonoperative treatment consisted of the use of a plaster cast, with the fracture being reduced under local anesthesia if necessary. Operative treatment varied and was applied at the surgeon’s discretion.

After informed consent had been obtained, the protocol was initiated in the emergency department. Patients were asked to start the trial medication from that moment, on the day of the fracture. This medication was delivered in a box containing 100 capsules, with two capsules to be taken once daily for fifty days. Patients were allocated randomly to receive either placebo or a dosage of 200, 500, or 1500 mg of vitamin C daily.

The pharmacist in one of the participating hospitals, who also made up the medication for the other hospitals, executed the randomization in block form, with blocks of ten according to a table of random numbers. All capsules had the same appearance and taste. The trial was double-blind, with the pharmacist being the only individual with access to the code until the conclusion of the trial.

The endpoint of the study was defined as the presence of complex regional pain syndrome at any time within one year after the fracture. All participants and physicians were unaware of the treatment allocation. Complex regional pain syndrome was diagnosed by a physician in the treating department and not by anyone involved in the conduct of the trial.

At the time of enrollment, specific study parameters were recorded, including gender, age, the side of the fracture, dominance, fracture type according to the AO/ASIF classification system, dislocation, reduction, the number of the box containing the allocated treatment, drug intake, and the history with respect to previous wrist fractures or earlier episodes of complex regional pain syndrome.

Patients were evaluated after one week, four or five weeks (or when the cast was removed), six or seven weeks, twelve weeks, and twenty-six weeks. After one year, patients were interviewed by telephone or were sent an inquiry letter with a postage-paid envelope for their reply. Fracture treatment was not compromised by the protocol. If necessary, patients were seen more often and/or at other times. Attention was paid to early complaints related to the cast, such as pain, swelling, and numbness.

Complex regional pain syndrome type I was diagnosed if four of the following five symptoms were present at the wrist, including the area distal to the wrist (the hand and fingers), and if they occurred (or increased) after activity: (1) unexplained diffuse pain that was not normal in relation to the stage of fracture treatment, (2) a difference in skin color relative to the other hand and wrist, (3) diffuse edema, (4) a difference in skin temperature relative to the other hand and wrist, and (5) limited active range of motion of the wrist and fingers that was unrelated to the stage of fracture treatment.

If complex regional pain syndrome was diagnosed, the endpoint of the study was reached and the protocol was terminated to allow for the treatment of complex regional pain syndrome.

Statistical Analysis

Statistical analysis was performed with SPSS version 11.0 (SPSS, Chicago, Illinois) and MedCalc version 9.2 (MedCalc Software, Mariakerke, Belgium) software on a personal computer. Sample and group sizes were estimated a priori with use of results of our previous study, a planned power of 90%, and a significance level (α) of 0.05.

The chi-square test, analysis of variance, and the Student t test were used as applicable for univariate analysis. Measures of association, along with their confidence intervals, were calculated with the Pearson chi-square test or the Fisher exact test. The significant independent variables from the univariate analysis were entered in a multivariate logistic regression with the occurrence of complex regional pain syndrome as a dependent variable. The likelihood ratio backward test was conducted to find the best-fit model by selecting the variables one by one. The probability for entry was set at 0.05, and the probability for removal was set at 0.10.

Kaplan-Meier curves with 95% confidence intervals...
were generated to show the time between the fracture and the diagnosis of complex regional pain syndrome. The curves for the placebo and vitamin C groups were compared with use of a log-rank test.

**Results**

Between January 2001 and December 2004, we enrolled 416 patients with 427 fractures from a total population of 2137 patients with wrist fractures who presented to the three emergency departments at the three hospitals. The follow-up period ended in December 2005.

Ten patients had a bilateral fracture, and one had an ipsilateral refracture. All fractures were assessed individually. None of the randomized patients were excluded from the study. No adverse events occurred.

Randomization involved 416 patients from the three centers: 317 patients with 328 fractures received vitamin C, and ninety-nine patients with ninety-nine fractures received a placebo. The trial profile is shown in Figure 1. The 1721 patients who were excluded comprised 463 patients who refused to take part for various reasons, 297 patients who wanted to be sure that they received vitamin C, and 961 patients who had not been invited to take part in the study.

The patients who were given vitamin C and those who were given a placebo did not differ significantly in terms of demographic characteristics (Table I). Analysis of the groups receiving the three different doses of vitamin C and the placebo showed no significant differences with regard to gender, age, the side of the fracture, dominance, fracture type, dislocation, reduction, or treatment modality (Table I).

After one year, all patients were interviewed by telephone, with the exception of eighteen patients who received an inquiry letter and one patient who was visited at home. It was not necessary to see any of the patients in the outpatient

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**Fig. 1**

CONSORT E-Flowchart illustrating the trial profile. The CONSORT comprises a checklist and a flow diagram to help improve the quality of reports of randomized controlled trials, offering a standard way for researchers to report trials.
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Clinic again as there was no suspicion of a missed diagnosis of complex regional pain syndrome. None of the patients were lost to follow-up.

Twenty-five patients had been taking vitamin supplements prior to the fracture. Of these, nine had been taking vitamin B, two had been taking vitamin D, and thirteen had been taking a multivitamin preparation. None of those twenty-four patients had been consuming vitamin C in high doses (>50 mg daily, which is the recommended daily intake), and therefore none of them were excluded. The remaining patient had been taking 1000 mg of vitamin C daily. She was asked to stop taking this supplement during the trial. In retrospect, she was randomized to 1500 mg of vitamin C daily.

The prevalence of complex regional pain syndrome was 2.4% (eight of 328) in the vitamin C group and 10.1% (ten of ninety-nine) in the placebo group (p = 0.002) (Table I). All of the affected patients were elderly women. For the entire cohort, the prevalence of complex regional pain syndrome was 4.2% (eighteen of 427).

Analysis of the different doses of vitamin C showed that the prevalence of complex regional pain syndrome in the 200-mg group (4.2%; four of ninety-six) was lower than that among those in the placebo group (10.1%; ten of ninety-nine) (Table I), but this difference was not significant (relative risk, 0.41; 95% confidence interval, 0.13 to 1.27) (Table II). Significant differences were seen in the 500 (p = 0.007) and 1500-mg (p = 0.005) groups, in which the relative risks of complex regional pain syndrome were 0.17 (95% confidence interval, 0.04 to 0.77) and 0.17 (95% confidence interval, 0.04 to 0.75), respectively. Overall, there was a significant difference between the vi-
Vitamin C group and the placebo group (relative risk, 0.24; 95% confidence interval, 0.10 to 0.60) \( p = 0.002 \) (Table II).

In the present study, all patients with complex regional pain syndrome were female; for male patients, the relative risk that complex regional pain syndrome would not develop was 0.95 (95% confidence interval, 0.93 to 0.97). Complex regional pain syndrome occurred significantly more frequently in older patients (Table II).

One patient had a refracture and was randomized twice over an interval of four months, the first time to 500 mg and the second time to 1500 mg of vitamin C. Fracture treatment was nonoperative on both occasions, and complex regional pain syndrome did not develop.

One seventy-four-year-old patient in the 1500-mg vitamin C group who had a fracture of both wrists had development of complex regional pain syndrome on the right side, where she had a simple AO 23-A2-type fracture that had been inadequately reduced. On the left side, where the patient had an adequately reduced AO 23-A3-type fracture, there were no signs of complex regional pain syndrome.

Complex regional pain syndrome was not associated with the side of the fracture, dominance, the type of fracture, the need to undergo reduction, or the type of treatment (operative or nonoperative) (Table II).

Early complaints related to the plaster cast were predictive of the occurrence of complex regional pain syndrome (relative risk, 5.35; 95% confidence interval, 2.13 to 13.42) (Table II).

### Table II: Relative Risk of Complex Regional Pain Syndrome

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Complex Regional Pain Syndrome (N = 18)</th>
<th>No Complex Regional Pain Syndrome (N = 409)</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (no. of fractures)</td>
<td></td>
<td></td>
<td>0.95 (0.93 to 0.97)*</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>18 (100%)</td>
<td>334 (82%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0 (0%)</td>
<td>75 (18%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age† (yr)</td>
<td>67.6 ± 7.7</td>
<td>62.1 ± 17.4</td>
<td>0.96 (0.39 to 2.39)</td>
<td>0.011</td>
</tr>
<tr>
<td>Side of the fracture (no. of fractures)</td>
<td></td>
<td></td>
<td>1.14 (0.46 to 2.82)</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>8 (44%)</td>
<td>186 (45%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>10 (56%)</td>
<td>223 (55%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominance‡ (no. of fractures)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9 (50%)</td>
<td>190 (46%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>9 (50%)</td>
<td>218 (53%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fracture type (no. of fractures)</td>
<td></td>
<td></td>
<td>1.31 (0.48 to 3.6)</td>
<td>0.821</td>
</tr>
<tr>
<td>23-A</td>
<td>11 (61%)</td>
<td>220 (54%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23-B</td>
<td>3 (17%)</td>
<td>87 (21%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23-C</td>
<td>4 (22%)</td>
<td>102 (25%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dislocation (no. of fractures)</td>
<td></td>
<td></td>
<td>0.99 (0.39 to 2.5)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13 (72%)</td>
<td>271 (66%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5 (28%)</td>
<td>138 (34%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction (no. of fractures)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11 (61%)</td>
<td>251 (61%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>7 (39%)</td>
<td>158 (39%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cast-related complaints (no. of fractures)</td>
<td></td>
<td></td>
<td>5.35 (2.13 to 13.42)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>10 (56%)</td>
<td>89 (22%)</td>
<td>0.41 (0.13 to 1.27)</td>
<td></td>
</tr>
<tr>
<td>Vitamin C 200 mg</td>
<td>4 (22%)</td>
<td>92 (22%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin C 500 mg</td>
<td>2 (11%)</td>
<td>112 (27%)</td>
<td>0.17 (0.04 to 0.77)</td>
<td></td>
</tr>
<tr>
<td>Vitamin C 1500 mg</td>
<td>2 (11%)</td>
<td>116 (28%)</td>
<td>0.17 (0.04 to 0.75)</td>
<td></td>
</tr>
<tr>
<td>Vitamin C overall</td>
<td>8 (44%)</td>
<td>320 (78%)</td>
<td>0.24 (0.10 to 0.60)</td>
<td></td>
</tr>
<tr>
<td>Treatment (no. of fractures)</td>
<td></td>
<td></td>
<td>0.46 (0.06 to 3.41)</td>
<td></td>
</tr>
<tr>
<td>Conservative</td>
<td>17 (94%)</td>
<td>362 (89%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operative</td>
<td>1 (6%)</td>
<td>47 (11%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Relative risk calculated for no complex regional pain syndrome. †The values are given as the mean and the standard deviation. ‡This information was missing for one fracture. §Data on cast-related complaints were missing for fifteen fractures (with no complex regional pain syndrome), so this percentage is based on 394 fractures.
的风险，5.35；95% 置信区间，2.13 至 13.42）。总体，复杂区域疼痛综合征的诊断平均在骨折后 76 天（范围，30 至 166 天）（图 2）。诊断复杂区域疼痛综合征的时间在维生素 C 组患者较早（68 天相比 83 天），但这种差异不具统计学意义。

 Logistic 回归分析预测因素得到显著的 odds 比率为 5.73 (2.11 至 15.57) 以及 0.22 (0.08 至 0.58)（表 III）。

**Discussion**

该研究证实了维生素 C 可以抑制复杂区域疼痛综合征的发作后腕部骨折。需要提及一些限制条件。

研究中，参与研究的患者人数与腕部骨折的患者人数相比较少，但经过随机后没有任何患者丢失。在急诊室的环境中，很难让工作人员和患者有兴趣参加任何研究。可能缺乏兴趣解释了未被邀请患者的比例较高（961）。此外，知情同意过程中，患者被告知了我们以前的研究结果，这表明这些患者更愿意接受维生素 C。因此，297 名患者希望确保他们能够得到维生素 C 并决定不参与研究。

所有报告的置信区间均较宽，我们的分析基于我们的以前的研究，但目前研究中的复杂区域疼痛综合征的发病率低于预期。

在荷兰，维生素补充剂的摄入量正在稳步增加，但仍然较低。只有 25 名患者在骨折发生前已经服用过维生素补充剂，除了其中一位患者外（每天 50 mg 以上）。

研究的内部控制措施，包括随机化过程中的患者分组，以减少可能的偏倚。因此，可以基于我们的数据来评估维生素 C 的作用。

**Table III**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cast-related complaints</td>
<td>5.73 (2.11 to 15.57)</td>
<td>0.001</td>
</tr>
<tr>
<td>Vitamin C overall</td>
<td>0.22 (0.08 to 0.58)</td>
<td>0.020</td>
</tr>
<tr>
<td>Vitamin C 200 mg</td>
<td>0.38 (0.11 to 1.30)</td>
<td>0.122</td>
</tr>
<tr>
<td>Vitamin C 500 mg</td>
<td>0.14 (0.03 to 0.68)</td>
<td>0.014</td>
</tr>
<tr>
<td>Vitamin C 1500 mg</td>
<td>0.16 (0.03 to 0.77)</td>
<td>0.022</td>
</tr>
</tbody>
</table>

The Kaplan-Meier survival curves (with 95% confidence intervals) for the vitamin C and placebo groups, with the occurrence of complex regional pain syndrome (CRPS) as the end point. 0 = placebo, 1 = vitamin C, and df = degrees of freedom.
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The overall prevalence of complex regional pain syndrome in the present study was 4.2%, and the prevalence for the placebo group was 10.1%. This rate in the placebo group is lower than those in our previous study (22%) and in the studies reported by Atkins et al. (25% and 37%, respectively). A possible explanation for the lower prevalence in the present study might be found in the more precise criteria (as described by Veldman et al.) that we used for the diagnosis of complex regional pain syndrome. In the present study the diagnosis was made if four of five symptoms were present, whereas in our previous study the diagnosis was made if four of six symptoms were present.Clinicians in The Netherlands are more acquainted with the criteria of Veldman et al. than they are with other criteria such as those from the International Association for the Study of Pain (the so-called IASP criteria) or the modified research criteria proposed by Bruehl and others. Another reason for the lower prevalence might be the fact that surgically treated fractures were included in the present study. The number needed to treat (NNT) was 12 for the 500-mg dose of vitamin C in this study.

We found that complaints related to the use of the plaster cast were strongly predictive of the development of complex regional pain syndrome. This finding has been described in previous studies and should alert physicians who treat fractures with a plaster cast. In the present study, all patients with complex regional pain syndrome were female, and this was significant in univariate analysis. From this observation that complex regional pain syndrome occurs more often in elderly women, the suggestion has been made that estrogen status could be a confounding factor.

The mean time-interval between the wrist fracture and the diagnosis of complex regional pain syndrome was seventy-six days for all cases. The mean interval was sixty-eight days for patients in the vitamin C group and eighty-three days for patients in the placebo group. The length of this time-interval is consistent with the results reported by Geertzen et al., who reported a mean interval of 2.3 months for the development of upper limb complex regional pain syndrome resulting from various causes.

The pharmacodynamic behavior of vitamin C in the treatment of fracture or the prevention of complex regional pain syndrome is not fully understood. Nevertheless, previous studies have shown a positive effect of vitamin C in different healing processes. Yilmaz et al., in a study of experimental fractures in rats, suggested that vitamin C enhanced fracture-healing in comparison with that in a control group, and Sarisozen et al. confirmed that vitamin C accelerated fracture-healing in rats. We did not study the time needed for fracture-healing.

Ischemia-reperfusion injury is caused by endothelial and subendothelial damage by neutrophil-derived oxidants. Kearns et al. noted that pretreatment with oral vitamin C protected against this injury in rats, possibly by diminishing neutrophil respiratory burst activity. In a later study, they provided experimental evidence of a potential role for antioxidants, such as vitamin C, in the reduction of injury to skeletal muscle caused by compartment syndrome. With the knowledge that the production of oxidants in neutrophils is reduced by the administration of vitamin C and that vitamin C can protect the endothelium from direct injury by oxidants, one can postulate that it can prevent microvascular dysfunction and the microangiopathy of an inflammatory reaction as is seen in complex regional pain syndrome.

The strength of our conclusion is limited by two issues. First, our two vitamin C studies yielded relative risks with wide confidence intervals, which must be interpreted as a lack of precision, limiting the validity of our conclusion. Second, with vitamin C, we prevented a group of symptoms defined by us as complex regional pain syndrome. Due to the lack of precision with this diagnosis, we cannot be sure that we actually prevented complex regional pain syndrome.

In conclusion, we recommend the administration of 500 mg of vitamin C daily for fifty days after a wrist fracture because we believe that such treatment may prevent complex regional pain syndrome. Whether vitamin C can also be used as a treatment for complex regional pain syndrome should be the subject of further study.

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P.E. Zollinger, MD
Department of Orthopaedic Surgery, Ziekenhuis Rivierenland, President Kennedylaan 1, 4002 WP Tiel, The Netherlands. E-mail address: PE.Zollinger@tiscali.nl

W.E. Tuinebreijer, MD, PhD, MSc, MA
Relweg 59, 1949 EC Wijk aan Zee, The Netherlands

R.S. Breederveld, MD, PhD
R.W. Kreis, MD, PhD
Departments of Surgery (R.S.B., R.W.K.) and Burn Wounds (R.W.K.), Red Cross Hospital, Vondellaan 13, 1942 LE Beverwijk, The Netherlands
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