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Can Vitamin C Prevent Complex Regional Pain Syndrome in Patients with Wrist Fractures?

A Randomized, Controlled, Multicenter Dose-Response Study

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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 syndrome¹. 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 mediators². 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 microangiopathy³. 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 edema⁴. 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^{2,3}. 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 fractures³. 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 reported⁵. 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 end point 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 system⁶, 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 treatment⁷.

If complex regional pain syndrome was diagnosed, the end point 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 0.05³.

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

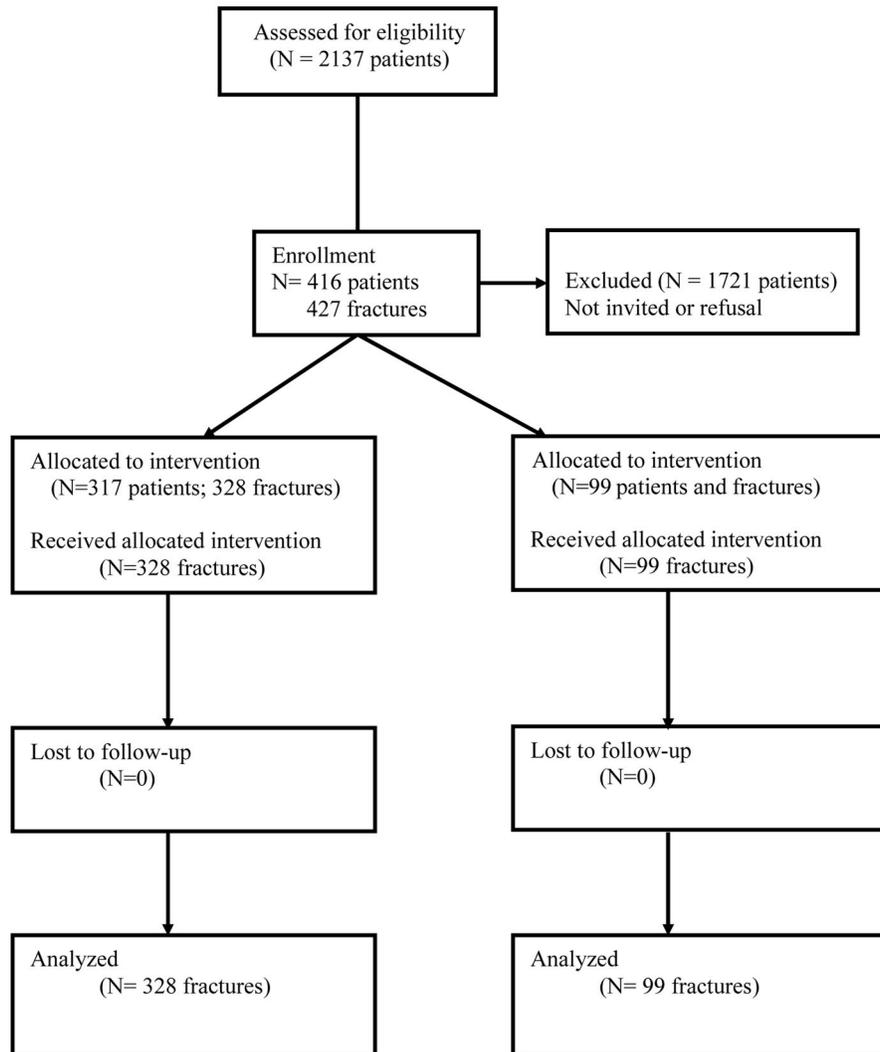


Fig. 1

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.

TABLE I Demographic Data

	Vitamin C 200 mg (N = 96)	Vitamin C 500 mg (N = 114)	Vitamin C 1500 mg (N = 118)	Placebo (N = 99)	Vitamin C 200 mg, 500 mg, 1500 mg (N = 328)	P Value†	P Value‡
Gender (<i>no. of fractures</i>)						0.796	0.431
Female	80 (83%)	93 (82%)	100 (85%)	79 (80%)	273 (83%)		
Male	16 (17%)	21 (18%)	18 (15%)	20 (20%)	55 (17%)		
Age* (<i>yr</i>)	62.8 ± 17.2	62.8 ± 15.0	62.4 ± 18.3	61.4 ± 18	62.7 ± 16.8	0.930	0.522
Side of the fracture (<i>no. of fractures</i>)						0.905	0.996
Right	42 (44%)	55 (48%)	52 (44%)	45 (45%)	149 (45%)		
Left	54 (56%)	59 (52%)	66 (56%)	54 (55%)	179 (55%)		
Dominance§ (<i>no. of fractures</i>)						0.946	0.687
Yes	46 (48%)	51 (45%)	54 (46%)	48 (48%)	151 (46%)		
No	50 (52%)	63 (55%)	63 (54%)	51 (52%)	176 (54%)		
Fracture type (<i>no. of fractures</i>)						0.571	0.447
23-A	57 (59%)	65 (57%)	57 (48%)	52 (53%)	179 (55%)		
23-B	20 (21%)	23 (20%)	29 (25%)	18 (18%)	72 (22%)		
23-C	19 (20%)	26 (23%)	32 (27%)	29 (29%)	77 (23%)		
Dislocation (<i>no. of fractures</i>)						0.524	0.970
Yes	58 (60%)	79 (69%)	81 (69%)	66 (67%)	218 (66%)		
No	38 (40%)	35 (31%)	37 (31%)	33 (33%)	110 (34%)		
Reduction (<i>no. of fractures</i>)						0.150	0.861
Yes	50 (52%)	76 (67%)	76 (64%)	60 (61%)	202 (62%)		
No	46 (48%)	38 (33%)	42 (36%)	39 (39%)	126 (38%)		
Treatment (<i>no. of fractures</i>)						0.891	0.963
Conservative	86 (90%)	99 (87%)	106 (90%)	88 (89%)	291 (89%)		
Operative	10 (10%)	15 (13%)	12 (10%)	11 (11%)	37 (11%)		
Complex regional pain syndrome (<i>no. of fractures</i>)						0.007	0.002
Yes	4 (4%)	2 (2%)	2 (2%)	10 (10%)	8 (2.4%)		
No	92 (96%)	112 (98%)	116 (98%)	89 (90%)	320 (97.6%)		

*The values are given as the mean and the standard deviation. †Placebo group compared with the three different vitamin-C groups. ‡Placebo group compared with overall vitamin-C group. §This information was missing for one fracture.

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-

tamin 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

TABLE II Relative Risk of Complex Regional Pain Syndrome

Characteristic	Complex Regional Pain Syndrome (N = 18)	No Complex Regional Pain Syndrome (N = 409)	Relative Risk (95% Confidence Interval)	P Value
Gender (<i>no. of fractures</i>)			0.95 (0.93 to 0.97)*	
Female	18 (100%)	334 (82%)		
Male	0 (0%)	75 (18%)		
Age† (<i>yr</i>)	67.6 ± 7.7	62.1 ± 17.4		0.011
Side of the fracture (<i>no. of fractures</i>)			0.96 (0.39 to 2.39)	
Right	8 (44%)	186 (45%)		
Left	10 (56%)	223 (55%)		
Dominance‡ (<i>no. of fractures</i>)			1.14 (0.46 to 2.82)	
Yes	9 (50%)	190 (46%)		
No	9 (50%)	218 (53%)		
Fracture type (<i>no. of fractures</i>)				0.821
23-A	11 (61%)	220 (54%)		
23-B	3 (17%)	87 (21%)		
23-C	4 (22%)	102 (25%)		
Dislocation (<i>no. of fractures</i>)			1.31 (0.48 to 3.6)	
Yes	13 (72%)	271 (66%)		
No	5 (28%)	138 (34%)		
Reduction (<i>no. of fractures</i>)			0.99 (0.39 to 2.5)	
Yes	11 (61%)	251 (61%)		
No	7 (39%)	158 (39%)		
Cast-related complaints (<i>no. of fractures</i>)	11 (61%)	86 (22%)§	5.35 (2.13 to 13.42)	
Prevention (<i>no. of fractures</i>)				
Placebo	10 (56%)	89 (22%)		
Vitamin C 200 mg	4 (22%)	92 (22%)	0.41 (0.13 to 1.27)	
Vitamin C 500 mg	2 (11%)	112 (27%)	0.17 (0.04 to 0.77)	
Vitamin C 1500 mg	2 (11%)	116 (28%)	0.17 (0.04 to 0.75)	
Vitamin C overall	8 (44%)	320 (78%)	0.24 (0.10 to 0.60)	
Treatment (<i>no. of fractures</i>)			0.46 (0.06 to 3.41)	
Conservative	17 (94%)	362 (89%)		
Operative	1 (6%)	47 (11%)		

*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.

TABLE III Results of Logistic Regression Analysis

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

risk, 5.35; 95% confidence interval, 2.13 to 13.42). Overall, complex regional pain syndrome was diagnosed at an average of seventy-six days (range, thirty to 166 days) after the fracture (Fig. 2). The diagnosis of complex regional pain syndrome was made earlier for the patients in the vitamin C group than for those in the placebo group (sixty-eight compared with eighty-three days), but this difference was not significant.

The logistic regression analysis of the predictive factors yielded significant odds ratios for cast-related complaints and vitamin C doses of 500 and 1500 mg daily (Table III).

Discussion

The present study confirms that vitamin C can have an inhibiting effect on the occurrence of complex regional pain syndrome after wrist fractures. Some limitations of the study should be mentioned.

The number of patients enrolled in the study was low in relation to the number of eligible patients who presented with

wrist fractures, but after randomization no patient was lost to follow-up. It is difficult in an emergency department setting to motivate staff and patients to participate in any study. The possible lack of interest explains the high number of uninvited patients (961). Furthermore, during the informed-consent process, patients were informed about our previous study³, which showed a positive effect of vitamin C. Therefore, 297 patients wanted to be sure that they received vitamin C and decided not to participate in the study.

The confidence intervals for all reported values were wide. Our power analysis was based on our previous study³, but the prevalence of complex regional pain syndrome in the present study was lower than expected.

In The Netherlands, the intake of vitamin supplements is slowly increasing but is still low. Only twenty-five patients had already been taking vitamin supplements before the occurrence of the wrist fracture. None of them had been taking high-dose vitamin C (>50 mg daily) (except for the patient

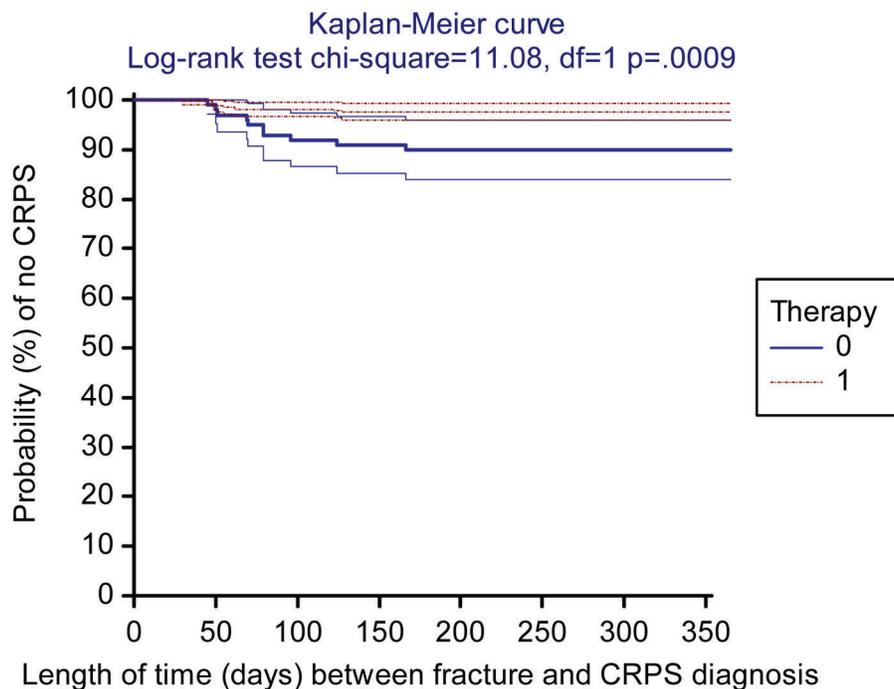


Fig. 2

Kaplan-Meier survivorship 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.

mentioned earlier, who had been asked to stop doing so), and therefore none of those patients were excluded. Because of the low numbers of patients who were known to have been taking supplements before the fracture and the high doses that were used in the study, this source of bias was limited. It is known that vitamin C rapidly reaches a steady state in human plasma at doses of >200 mg per day⁵. With a normal dietary intake of 50 to 60 mg of vitamin C per day added to our trial doses, we did not believe that there was a need to measure plasma levels of vitamin C. Compliance with taking the vitamins as recommended was not confirmed; however, all patients stated that they had consumed all fifty doses.

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 study³ (22%) and in the studies reported by Atkins et al.^{8,9} (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.⁷) 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.⁷ 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^{10,11}. Another reason for the lower prevalence might be the fact that surgically treated wrist 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^{3,12} 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 factor³.

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 causes¹³.

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 group¹⁴, and Sarisozen et al. confirmed that vitamin C accelerated fracture-healing in rats¹⁵. We did not study the time needed for fracture-healing.

Ischemia-reperfusion injury is caused by endothelial and subendothelial damage by neutrophil-derived oxidants⁵. Kearns et al. noted that pretreatment with oral vitamin C protected against this injury in rats, possibly by diminishing neutrophil respiratory burst activity⁵. 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 syndrome¹⁶. 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^{2,17-20}.

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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