

The Administration of Vitamin C in Prevention of CRPS-I After Distal Radial Fractures and Hand Surgery – A Review of Two RCTs and One Observational Prospective Study

Paul E. Zollinger*

Department of Orthopaedic Surgery and Traumatology, Ziekenhuis Rivierenland, Pres. Kennedylaan 1, 4002 WP Tiel, The Netherlands

Abstract: Complex regional pain syndrome type I (CRPS-I) is an affliction that can occur after trauma to an arm or leg. It is characterized by a combination of autonomous, sensory and vasomotor symptoms.

The pathogenesis of CRPS is not clear, nor is there a definitive treatment for this syndrome. The morbidity and costs in health care justify the search for a means to prevent CRPS. The diagnosis is made clinically and CRPS occurs relatively frequently after wrist fractures and most often in females.

Vitamin C (ascorbic acid) is a watersoluble vitamin that protects against scurvy and it acts as a strong anti-oxidant. By scavenging radicals, vitamin C halts free-radical reactions and prevents the propagation of chain reactions. In this way vitamin C protects the capillary endothelium and circulating cells.

The results of our two RCTs comparing vitamin C and placebo in the prevention of CRPS after distal radial fractures, were pooled for the analysis of the occurrence of CRPS. It is concluded that vitamin C reduces the chance on the occurrence of CRPS-I after wrist fractures, if it is started on the day of the fracture in a dose of 500 mg per day during 50 days.

Keywords: Ascorbic acid, CMC I prosthesis, reflex sympathetic dystrophy, wrist fracture, complex regional pain syndrome, trapeziometacarpal arthritis, joint replacement, vitamin C.

INTRODUCTION

Complex regional pain syndrome type I (CRPS-I) or Reflex Sympathetic Dystrophy (RSD) is an affliction that can occur after trauma to an arm or leg. It is characterized by a combination of autonomous, sensory and vasomotor symptoms. Pain, temperature difference, restricted motion, colour change, hyperaesthesia, hyperalgesia, hyperpathy, tremor, involuntary movement, muscle spasms, paresis, pseudoparalysis, atrophy of skin, muscle and bone, hyperhidrosis and changes in hair and nail growth have all been described.

A variety of terms are used for CRPS-I or RSD, including post-traumatic dystrophy, causalgia of Mitchell, and Sudeck's atrophy [1,2].

The pathogenesis of CRPS is not clear, nor is there a definitive treatment for this syndrome. The morbidity, costs in health care, and loss of working time justify the search for a means to prevent post-traumatic dystrophy.

The diagnosis of CRPS-I is a clinical one. There is no single, universally adopted set of criteria to diagnose CRPS, but in the Netherlands the Veldman criteria are preferred to the criteria of the International Association for the Study of Pain (IASP)[3,4]. These IASP criteria draw a distinction

between CRPS type I (the classical RSD), where no nerve damage is found, and type II, where nerve damage can be demonstrated (known as causalgia).

The incidence of CRPS may have been underestimated. Sandroni *et al.* found in the Olmsted County study an incidence of 5.46 per 100,000 person years, whereas De Mos *et al.* in the Netherlands described an incidence of 26.2 per 100,000 person years [5,6].

Wrist fractures are a common condition and can be sustained by anyone in daily life.

The management of distal radial fractures is in most cases conservative. Patients are treated with a plaster of Paris cast or splint, after reduction if necessary. If conservative treatment of a wrist fracture is not possible, closed reduction with external fixation, closed reduction with internal fixation or open reduction with internal fixation can be the choice of treatment. K-wires can also be used according to Kapandji [7].

In some cases after a distal radial fracture CRPS type I will develop. When CRPS occurs, however, the condition may develop into a chronic disability, meaning that the simple wrist fracture is no longer marginal for the patient in question, his relatives, social and working environment.

In literature a broad variation exists of the incidence of CRPS after wrist fractures from 1% up to 37% [8,9]. In an earlier report we described an incidence of 22% in a control

*Address correspondence to this author at the Department of Orthopaedic Surgery and Traumatology, Ziekenhuis Rivierenland, Pres. Kennedylaan 1, 4002 WP Tiel, The Netherlands; Tel: +31344674911; Fax: +31344632903; E-mail: P.E.Zollinger@zrt.nl

group [10]. As we are lacking a real cure for CRPS, the emphasis of treatment should lie in prevention.

Vitamin C (ascorbic acid) is a watersoluble vitamin that protects against scurvy and it acts as a strong anti-oxidant. By scavenging radicals, vitamin C halts free-radical reactions and prevents the propagation of chain reactions. In this way vitamin C protects the capillary endothelium and circulating cells.

METHODS

Study Design

In the Netherlands the criteria of Veldman are mostly used these to establish the diagnosis of CRPS-I [3]. The reason for this is that the Veldman criteria are an empirically derived classification from a cohort of 829 patients [3]. The IASP criteria are the consensus result from expert opinions, but unfortunately they lack specificity [4].

Complex regional pain syndrome type I was diagnosed when four of the following five symptoms were present at the wrist, including the area distal to the wrist (hand and fingers), and if they occurred (or increased) after activity:

1. unexplained diffuse pain, not in normal relation to the stage of fracture treatment;
2. difference in skin colour relative to the other hand and wrist;
3. diffuse oedema;
4. difference in skin temperature relative to the other hand and wrist;
5. limited active range of motion of the wrist and fingers, unrelated to the stage of fracture treatment [3].

The original diagnostic criteria of the International Association for the Study of Pain (IASP) for CRPS-I are:

1. The presence of an initiating noxious event, or a cause of immobilization
2. Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event.
3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain.
4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction (Note: Criteria 2-4 must be satisfied).

CRPS-II develops after a nerve injury [4].

The diagnosis of CRPS was made by a physician in the treating department and not by anyone involved in the conduct of the trial. In these studies all the patients with CRPS had pain.

Statistical Analysis

The statistical analysis was performed with SPSS (during time versions 7.5, 11.0 and 15.0.1) software on a personal computer. Sample and group sizes were estimated a priori

using results of our previous study, a planned power of 90% and a significance (α) of 0.05 [3].

The chi-square test, Likelihood ratio test, Fisher's exact test, ANOVA and Student's t test were used as applicable for univariate analysis.

The paired t-test, Wilcoxon signed rank test and the Mann-Whitney U test were used as applicable for univariate analysis as well.

Review Manager 4.2 (The Cochrane Collaboration, 2003) was used for analysis forest plots.

A review is presented of a randomised controlled trial and a RCT in the format of a multicenter dose response study, which investigated the effect of three different doses of vitamin C on the incidence of CRPS-I [10, 11].

In case of an undisplaced distal radial fracture, the patient was treated with a cast for four weeks. A wrist fracture with a dislocation, was conservatively treated by a reduction under local anesthesia and a plaster of Paris during five weeks. In the second RCT some patients with a distal radial fracture were operated.

RESULTS

Two Randomized Clinical Trials

The results of our first randomized clinical trial (RCT) are described here [10].

As there was evidence of a successful influence of high doses of vitamin C in burn resuscitation, we set up a study to investigate this in wrist fractures in order to prevent CRPS. Our hypothesis was that the incidence of posttraumatic RSD after wrist fractures would be lower in the group receiving vitamin C than in a placebo group.

Between July 1995, and August 1997, 123 adults with 127 conservatively treated wrist fractures were randomly allocated in a double-blind trial to take a capsule of 500 mg vitamin C or placebo daily for 50 days. Each participant's sex, age, side of fracture, dominance, fracture type, dislocation, reduction and complaints with the plaster cast were recorded, and they were clinically scored for RSD. The follow-up lasted 1 year.

52 patients with 54 fractures (male 22%, female 78%; mean age 57 years) received vitamin C and 63 patients with 65 fractures (male 20%, female 80%; mean age 60 years) received placebo. CRPS occurred in four (7%) wrists in the vitamin C group and 14 (22%) in the placebo group. Risk difference is 15% (95% CI for differences 2-26). Number needed to treat (NNT) is 7. Other significant prognostic variables for the occurrence of CRPS were complaints while wearing the cast (relative risk 0.17 [0.07-0.41]) and fracture type (0.37 [0.16-0.89]). This prospective, double-blind study showed that vitamin C is associated with a lower risk of CRPS after wrist fractures.

The second RCT is our multicenter study [11]. By that time we knew that vitamin C inhibits vascular permeability and protects the endothelium and may prevent microvascular dysfunction and the microangiopathy of an inflammatory reaction, as in CRPS [12]. A steady state in human plasma at doses of > 200 mg of ascorbic acid (vitamin C) per day have been reported [13, 14]. To investigate a dose relation, we set

up a multicenter, placebo-controlled dose-response study with vitamin C for all types of wrist fractures with conservative and operative fracture treatment.

Between January 2001 and December 2004, 416 patients with 427 wrist fractures entered a double-blind, prospective, multicenter trial, with random allocation to treatment with placebo or with 200, 500, or 1500 mg of vitamin C daily for fifty days.

Three hundred and seventeen patients with 328 fractures were randomized to receive vitamin C, and ninety-nine patients with 99 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 affected patients were elderly women. Analysis of the different doses of vitamin C showed that the prevalence of CRPS 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 CRPS (relative risk, 5.35; 95% confidence interval, 2.13-13.42).

The NNT is 12. We conclude that vitamin C reduces the prevalence of complex regional pain syndrome after wrist fractures and we recommend the administration of a daily dose of 500 mg vitamin C for 50 days.

The results of these two randomized clinical trials comparing vitamin C and placebo in the prevention of CRPS (Zollinger *et al.*, 1999 and 2007) were pooled for the analysis of the occurrence of CRPS [10, 11]. Review Manager 4.2 (The Cochrane Collaboration, 2003) was used for analysis and creation of the forest plots. CRPS was less frequent in the vitamin C group (Relative risk 0.28, 95% Confidence interval 0.14 to 0.56; $p=0.0003$). A fixed effects model was used. The test for heterogeneity was not significant ($p=0.61$). But even if a random-effects model was used, the conclusions remained the same.

The second pooled outcome was the relative risk for CRPS in patients with or without cast-related complaints. In patients with these complaints the risk of CRPS was higher than in patients without them (Relative risk 3.20, 95% Confidence interval 2.31 to 4.43; $p<0.00001$).

The third pooled outcome was the relative risk of CRPS in female patients compared to males. In female patients the risk of CRPS was higher than in males (Relative risk 1.20, 95% Confidence interval 1.12 to 1.30; $p<0.00001$).

The advantage of the pooled relative risk is the narrower confidence interval as compared to the relative risks of the separate studies, which points to a greater precision. The pooled relative risk is a better approximation of the population relative risk.

An Observational Prospective Study

Furthermore we investigated prospectively our results after a total joint prosthesis for basal joint arthritis of the thumb under vitamin C prophylaxis [15].

Patients with trapeziometacarpal arthritis stage II or III according to Dell, and no benefit from conservative treatment, were selected to undergo joint replacement with a semi-constrained hydroxyapatite coated prosthesis [16].

First web opening and visual analogue scale (VAS) scores for pain, activities of daily living (ADL) and satisfaction were taken pre- and postoperatively [17]. Vitamin C 500 mg daily was started two days prior to surgery during 50 days as prevention for CRPS. Post-operative treatment was functional.

We performed 40 implantations for trapeziometacarpal arthritis in 34 patients (mean age 60.8 years; 27 females, 7 males) with a mean follow-up of 44 months. Operations were performed in day care under regional (or general) anesthesia.

First web opening increased with 15.4 degrees and there was a significant improvement for pain, ADL and satisfaction as well ($p = 0.000$). Patient satisfaction was strongly associated with the amount of pain reduction. According to the Veldman and IASP criteria, there were no cases of CRPS [3,4].

Torrededia *et al.* reported 5 cases of CRPS (13%) after 38 operations with the same implant we used in our study (Roseland prosthesis, DePuy International Ltd, Leeds, England) [18].

DISCUSSION

Part of the problem remains of course the way the diagnosis of CRPS is made or how it is classified [19]. A golden standard for the diagnosis of CRPS does not exist. Different criteria are used worldwide to describe CRPS type I, formerly known as reflex sympathetic dystrophy (RSD) [3,4]. There are only few evidence based therapeutic measurements for CRPS and no other prophylactics beside ascorbic acid have been described [19].

The rationale for the duration of 50 days (7 weeks) of prophylactic vitamin C intake, was determined as two weeks longer than our longest immobilization in a plaster cast (5 weeks). Cast complaints were addressed by the cast technician according to their standards, hopefully leading to a decrease in the chance of developing CRPS. Either the cast was loosened up or changed by a new one.

Then there are different ways in the treatment of a distal radial fracture. In general in literature an increase for surgical treatment of distal radial fractures is recognized. As there are no universally accepted criteria for an adequate reduction in displaced wrist fractures, the indication for conservative treatment is floating away towards the direction of surgical treatment. Volar plate fixation with locking plates is becoming popular. While plate fixation may allow earlier motion than six weeks of cast immobilization, no differences in motion, pain, strength or function were seen after three or six months postoperatively according to a review by Amadio in 2008 [20]. It has often been suggested that CRPS has a higher incidence after an external fixator, than after other methods of operative treatment, but we did not encounter that in our own study [21].

The prevalence for basal joint arthritis of the thumb is highest in women. After any type of surgery for basal joint

arthritis of the thumb complex regional pain syndrome (CRPS) type I may occur as a complication and this may vary from 8% to 19% [22-24]. Because of the small numbers of our intervention we lack a control group. Therefore we made a historical comparison with a similar cohort. We compared our outcome with the 13% CRPS Torrededia *et al.* (2006) reported retrospectively about their results after 38 implantations in 34 patients with the same implant we used. The diagnosis of CRPS was made by one of the orthopaedic surgeons in our department, introducing another possible bias. The comparison of these two studies results in a significant difference in the prevalence of CRPS {Relative Risk (RR) = 0.87; Confidence interval 0.77-0.98; p = 0.02}[15]. Despite these biases, we would still like to advise, in the absence of any other prophylactic, vitamin C as prophylaxis against CRPS in this type of trapeziometacarpal joint replacement.

CONCLUSION

After the pooling of both RCTs we conclude that vitamin C reduces the chance of the occurrence of complex regional pain syndrome type I (CRPS-I) after distal radial fractures, if 500 mg ascorbic is started once daily on the day of the fracture and continued during 50 days.

Furthermore we advise, in absence of any other prophylactic against CRPS, for elective hand surgery to start the same vitamin C regime two days prior to trapeziometacarpal joint replacement.

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