Vitamin C for prevention of CRPS-I in traumatology and orthopaedic surgery

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Chapter 9 - Summary

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Introduction (from Chapters 1, 2 and 4)

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. 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). These IASP criteria draw a distinction between CRPS type I (RSD), where no nerve damage is found, and type II, where nerve damage can be demonstrated (causalgia). Wrist fractures are a common condition and can be sustained by anyone in daily life. 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. The emphasis of treatment should be on prevention.

The association between the phenomena of inflammatory response in the first phase of burn treatment and RSD was made in the Red Cross Hospital in Beverwijk. In line with this, Goris proposed RSD as a model of a severe regional inflammatory response syndrome.

CHAPTER 2 is an outline of the clinical practice guideline 'Complex regional pain syndrome type I' (www.cbo.nl). The development of this evidence-based multidisciplinary guideline started in 2003 at the initiative of the Netherlands Society of Rehabilitation Specialists and the Netherlands Society of Anaesthesiologists under the auspices of the Institute for Healthcare Improvement, CBO.

The diagnosis of CRPS-I is based on the clinical observation of signs and symptoms. Clinical diagnosis of CRPS-I can be established on the basis of criteria published by Veldman and the IASP.

For pain treatment, the WHO analgesic ladder is advised up to step 2. In case of pain of neuropathic nature, anticonvulsants and tricyclic antidepressants may be considered.

For the treatment of inflammatory symptoms, free-radical scavengers are advised. Dimethylsulphoxide (DMSO) cream 50% 5 dd may be considered for patients who have suffered CRPS-I for less than one year. Acetylcysteine may be considered for CRPS-I patients with a primary cold skin temperature. Percutaneous sympathetic blockades may be used for a cold extremity if vasodilatory medication produces insufficient effect.

To decrease functional limitations, standardized physiotherapy and occupational therapy are advised. CRPS-I occurs relatively frequent after a wrist fracture. It has been demonstrated that oral administration of vitamin C 500 mg daily for 50 days reduces the risk of CRPS-I in patients after a wrist fracture. The use of vitamin C is recommended as a prophylactic for wrist fracture patients.

CRPS-I is less prevalent in children than in adults. Physiotherapy and occupational therapy, as part of a multidisciplinary approach, are advised in the treatment of children with CRPS-I. A protective and therapeutic effect of mannitol in CRPS-I has not been demonstrated.

CHAPTER 3 describes the chemical, pharmacodynamic and clinical aspects of vitamin C (ascorbic acid). Ascorbic acid is a water soluble vitamin and an organic acid that protects against scurvy.

Normal plasma concentrations of ascorbic acid are about 10-20 µg/ml; plasma concentrations below 1-1.5 µg/ml are associated with scurvy. Scurvy in turn is associated with a defect in collagen synthesis that is apparent by the failure of wounds to heal, in defects in tooth formation, and in rupture of capillaries, leading to numerous petechiae and their coalescence to form ecchymoses. Total body stores of ascorbic acid have been estimated to be about 1.5 g with a 30-45 mg daily turnover. Clinical signs of scurvy usually become evident after 3-5 months of deficient ascorbic acid intake - the total body store of vitamin C is then reduced to about 300 mg. Daily ingestion of 5-10 mg provides a total body store of 600 to 1000 mg of ascorbate. When 60 mg of vitamin C is used per day (the recommended dietary allowance [RDA] for adults) the concentration in plasma reaches about 8 µg/ml and the body store is around 1500 mg. The $t_{½}$ for vitamin C in humans is 16 days. Bioavailability is complete for 200 mg as a single dose, corresponding to the upper portion of the sigmoid curve that was found between dose and steady-state plasma concentration. A steady state in human plasma occurs at doses greater than 200 mg ascorbic acid (vitamin C) per day. 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. Administration of high-dose ascorbic acid during the first 24 hours after thermal injury significantly reduces resuscitation fluid volume requirements, body weight gain and wound oedema. In these patients a reduction in the severity of respiratory dysfunction was also apparent. Trauma or injury consume large quantities of vitamin C in humans. Supplementation with vitamin C has been shown to protect against oxidant-mediated endothelial injury in vivo. Oral pretreatment with vitamin C significantly reduced the functional, immunological and microvascular (oedema) effects of ischaemia reperfusion injury. In a model of compartment syndrome it was shown that pretreatment with vitamin C preserved muscle function and reduced the infiltration of neutrophils and oedema. The results of two RCT's comparing vitamin C and placebo in the prevention of complex regional pain syndrome were pooled for the analysis of the occurrence of CRPS. It is con-

cluded that vitamin C reduces the chance of the occurrence of CRPS after wrist fractures, if vitamin C is started on the day of the fracture in a dose of 500 mg per day during 50 days. The second pooled outcome was the relative risk for CRPS in patients with or without cast-related complaints. The risk of CRPS was higher in patients with these complaints than without them. The third pooled outcome was the relative risk of CRPS in female patients compared to males. The risk of CRPS was higher in female patients than in males.

The results of our first randomized clinical trial (RCT) are reported in **CHAPTER 4**. 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). 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]).

In conclusion, this prospective, double-blind study shows that vitamin C is associated with a lower risk of CRPS after wrist fractures.

The second RCT is described in **CHAPTER 5**. Vitamin C inhibits vascular permeability and protects the endothelium and may prevent microvascular dysfunction and the microangiopathy of an inflammatory reaction, as in CRPS. A protective effect of ascorbic acid against CRPS and a steady state in human plasma at doses of > 200 mg of ascorbic acid (vitamin C) per day have been reported. 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).

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.

CHAPTER 6 describes a subgroup analysis from our second RCT (see chapter 5). 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 carried out. The subgroup consisted of operated distal radial fractures.

A great variation in incidence of CRPS after wrist fractures has been reported, ranging from 1% up to 37%. It has been suggested that external fixation might lead to a higher incidence of CRPS (from 10% to even 60% in one study). Part of the problem in diagnosing CRPS is that different criteria are used worldwide to describe the syndrome.

In our multicenter dose response study in which patients with distal radial fractures were randomly allocated to placebo or vitamin C in a daily dose of 200 mg, 500 mg or 1500 mg during 50 days, we analyzed an operated subgroup.

Between January 2001 and December 2004 we prospectively included 48 patients with fractures (out of 427 fractures) who had to undergo surgery of some sort (11.2%). Twenty-nine patients (60%) were treated with external fixation, 14 patients (29%) with K-wiring according to Kapandji and five patients (10%) with internal plate fixation. The 379 remaining patients were treated with a plaster.

In the operated group of patients who received vitamin C no CRPS (0/37) was seen in comparison with one case of CRPS in the operated group who received placebo (1/11 = 9%, p=0.23; a patient with Kapandji technique). There was no CRPS after external fixation.

In the conservatively treated group 17 cases of CRPS (17/379 = 4.5%) occurred in comparison with one in case of CRPS in the operated group (1/48 = 2.1%, p=0.71). External fixation does not necessarily lead to a higher incidence of CRPS in distal radial fractures. Vitamin C may also play a role here. The post-hoc calculated power for finding a difference between the proportion of CRPS in the operated vitamin C group (0/37= 0%) and the proportion of CRPS in the operated non-vitamin C group (1/11= 9.1%) was 26% (alpha .05).

This subgroup analysis in operated distal radial fractures with an external fixator showed no CRPS occurrence with vitamin C prophylaxis.

CHAPTER 7 describes a case report of a late reconstruction of a traumatic trapeziometacarpal dislocation with a semi-constrained prosthesis. Traumatic dislocation of the trapeziometacarpal joint is rare. A stable reduction should be accomplished as soon as possible, usually with K-wiring. In this case of persistent instability a semi-constrained prosthesis was applied. The operation was performed as a day case under plexus anaesthesia and vitamin C prophylaxis. A cementless total trapezio-metacarpal joint prosthesis (Roseland prosthesis) was implanted. This titanium alloy prosthesis has a partial hydroxyapatite coating and is semi-constrained. Postoperative treatment consisted of a plaster of Paris for 6 weeks. Six weeks later there was a stable situation, excellent function and high satisfaction rate, which persisted during the four years of follow-up. There were no signs of CRPS type I, nor did any other complication occur in that period.

CHAPTER 8 presents the results of a prospective study on trapeziometacarpal joint arthroplasty under vitamin C prophylaxis. Osteoarthritis of the trapeziometacarpal (TM) or first carpometacarpal joint (CMC I) is a common arthritic disease entity. Treatment is usually conservative. Possible surgical solutions are resection or interposition arthroplasty, fusion or arthrodesis and prosthetic joint replacement. These surgical procedures are associated with a high complication rate and complex regional pain syndrome (CRPS) type I might occur. From 2002 on we undertook a prospective cohort study under vitamin C prophylaxis and evaluated the clinical results after total joint arthroplasty.

Twenty-seven patients (21 females and 6 men) with trapeziometacarpal joint arthritis stage II or III (according to Dell) and no benefit from non-operative therapy were selected to undergo joint arthroplasty. Visual analogue scale (VAS) scores for pain, activities of daily living (ADL) and satisfaction were taken pre- and postoperatively, together with first web opening. Vitamin C 500 mg daily was started two days before surgery for a period of 50 days.

We performed 32 arthroplasties for first carpometacarpal arthritis in these 27 patients using a cementless total trapeziometacarpal joint prosthesis (Roseland type). The degree of osteoarthritis according to Dell was stage II in 13 cases and stage III in 18. One patient had a traumatic dislocation of the trapeziometacarpal joint (see chapter 7). VAS scores for pain, daily functioning and satisfaction improved significantly after operation ($p=0.000$, paired t-test). First web opening increased with 18^0 ($p=0.000$, paired t-test). Complications occurred in 5 of 32 surgical procedures (15.6%), without any infections. In three cases a revision (9.5%) to a resection arthroplasty was needed. We detected no cases of complex regional pain syndrome type I. The literature contains a report of a retrospective study with the same implant (N=38; no vitamin C prophylaxis), in which 5 cases of CRPS (13%) were recorded.