Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: a randomised trial

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Summary

Background The pathogenesis of reflex sympathetic dystrophy (RSD) is not clear, nor is there a definitive treatment for this syndrome. The morbidity, costs in health care, and loss of work time justify the search for a means to prevent post-traumatic dystrophy. Although the role of toxic oxygen radicals has not yet been clarified, we investigated vitamin C (ascorbic acid) as a prophylactic antioxidant drug.

Methods 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.

Findings Eight patients were withdrawn after randomisation. 52 patients with 54 fractures (male 22%, female 78%; mean age 57 years) received vitamin C and 63 patients with 65 fractures (male 20%,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. RSD occurred in four (7%) wrists in the vitamin C group and 14 (22%) in the placebo group 15% (95% CI for differences 2–26). Other significant prognostic variables for the occurrence of RSD were complaints while wearing the cast (relative risk 0·17 [0·07–0·41]) and fracture type (0·37 [0·16–0·89]).

Interpretation This prospective, double-blind study shows that vitamin C was associated with a lower risk of RSD after wrist fractures. Our hypothesis is that this beneficial effect of prophylaxis would be useful in other forms of trauma.

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Introduction

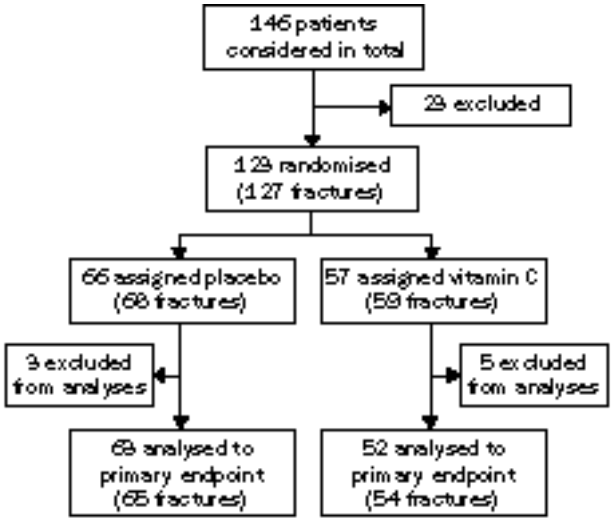
The pathogenesis and treatment of reflex sympathetic dystrophy (RSD) are still a matter of debate. The large number of names given to this syndrome, such as causalgia of Mitchell,[1] Sudeck's atrophy,[2] algodystrophy, post-traumatic RSD, and complex regional pain syndrome type 1, confirms that this subject is a puzzle to many investigators.

RSD is characterised by a pseudo-inflammatory hot phase and a cold phase. In the first phase, the primary changes to the tissue are caused by sympathetic microcirculatory disturbances,[3] whereas in the cold phase the tissue undergoes secondary trophic changes. The role of toxic oxygen radicals has been investigated in several studies.[4–6]

The morbidity of this syndrome, the costs in health care, and loss of working time justify the search for a preventive treatment. Research in burn injuries led us to try an antioxidant drug to prevent post-traumatic dystrophy. Matsuda and colleagues extensively investigated the effects of high-dose vitamin C therapy on dermal burns.[7–10] They found that vitamin C stops the progression of vascular permeability after burns[7] and therefore reduces microvascular leakage of fluid and protein.[8] Vitamin C also reduces lipid peroxidation after burns.[9] Lipid peroxidation damages the microvascular endothelial cells, thereby increasing capillary permeability. The lipid peroxide in the cell membrane can only be scavenged by vitamin E, the primary lipid-soluble small-molecule antioxidant,[11] producing a vitamin E free-radical complex.[12,13] In the extracellular fluid vitamin C, the terminal water-soluble small-molecule antioxidant,[11] acts on this complex and removes the free radical moiety, regenerating vitamin E.[14,15] Vitamin C is a natural antioxidant that can scavenge hydroxyl radicals[16] and superoxide radicals that produce hydroxyl radicals.[10,17] By scavenging these radicals, vitamin C stops free-radical reactions and prevents the propagation of chain reactions.[11–13] Thus, vitamin C protects the capillary endothelium and circulating cells such as erythrocytes and leucocytes.[10]

There are very few substances that have such an impact on wounds after burns and the signs of inflammation at that stage as vitamin C. The link between these experiments in burn wounds, an animal model of inducing RSD,[5] and patient studies[6,18] is an inflammatory component, and involvement of microangiopathy is suggested. Extrapolation of these results gave us the idea for the application of vitamin C as prophylaxis for RSD.

The recommended daily allowance of vitamin C is 60 mg according to the National Research Council of the USA. Healthy individuals need less vitamin C per day than those with chronic diseases.[19] As a prophylactic antioxidant we chose to administer ten times the daily dose recommended in the Netherlands and gave 500 mg ascorbic acid in a capsule. This amount is still far below the overdose level. Our hypothesis was that the frequency



Trial profile

of post-traumatic RSD after wrist fractures would be lower in the group receiving vitamin C than in a matched placebo group.

Patients and methods

Study design

We studied adults (aged 18 years or older) who were admitted to the emergency department of our hospital (Red Cross Hospital, Beverwijk, Netherlands) with a fracture of the wrist (or both wrists). Only patients with fractures that were to be treated conservatively (immobilisation by a plaster cast, after reduction under local anaesthesia, if necessary) were enrolled in the study. Fractures with unacceptable reduction or secondary dislocation were operated on and excluded from this study. Patients were asked to participate in this study and were given an information leaflet. The protocol was started after signature of the informed consent form.

On the day of the fracture, patients were asked to take one capsule daily for a period of 50 days. The patients were randomly allocated a box containing 50 capsules of either 500 mg vitamin C or placebo. A block randomisation (in blocks of ten at a time by a random number table) was done by the hospital pharmacist with the boxes containing the capsules. The capsules had to be swallowed whole and the vitamin C and placebo capsules had the same appearance and taste. The trial was double-blind. The pharmacist alone was in possession of the allocation code during the trial. The code was broken after the last follow-up control of 1 year. Our endpoint was defined as the presence or absence of RSD after 1 year. All the participants and physicians involved were unaware of the treatment allocation until the end of the trial.

The 50-day period of medication intake is 2 weeks longer than the usual time spent in plaster for a wrist fracture in our clinic, which is 5 weeks for a Colles' fracture (AO/ASIF classification 23-A2.2) or Smith's fracture (AO 23-A2.3).[20] Fractures that do not require reduction (AO 23-A2.1) are normally treated by 4 weeks of plaster immobilisation. The hospital ethics committee approved the study.

At intake, sex, age, side of fracture (right, left, or both), dominance, fracture type, dislocation, reduction, registration of the box, drug intake, history of wrist fractures, and earlier episodes of RSD were recorded.

Patients were assessed after 1 week, 4–5 weeks (when the plaster cast was removed), 6–7 weeks, 12 weeks, and 26 weeks. After 1 year we interviewed patients by telephone. Participation in the study did not affect the normal fracture treatment for the patient in any way. Particular attention was paid to early complaints when wearing the cast, such as pain, numbness, and swollen fingers. RSD was diagnosed[21] when four of the following six symptoms were present throughout an area larger than the wrist, including the area distal to the wrist: unexplained diffuse pain, which was not in normal relation to the fracture; difference in skin temperature relative to the other arm; difference in skin colour relative to the other arm; diffuse oedema; limited active range of motion, not in relation to the stage of fracture treatment; and occurrence or increase of these signs and symptoms after activity. If the diagnosis of RSD was established, the protocol was terminated, and patients were treated symptomatically.[22]

Statistical analysis

The χ^2 test, Kruskal-Wallis ANOVA, Mann-Whitney *U* test and Student's *t* test were used as applicable. Statistical analysis was done with the SPSS (version 7.5) software running on a personal computer. Measures of association with their CIs were calculated with Epitable. The likelihood step forward test was done to find the best fit model by selecting the variables one by one. Probability for entry was set at 0·05 and probability for removal 0·10.

Results

Between July, 1995, and August, 1997, 123 patients with 127 fractures of the wrist were enrolled. One patient had to be excluded because she had not taken any capsules. Seven others were excluded because they were operated on for unacceptable reduction or redislocation. The reason for the primary exclusion of 23 patients (of the original 146) was indication for reduction with fixation (external or internal), refusal of trial participation of the patients, and living elsewhere and therefore not being available for follow-up (figure). Thus, 115 patients with 119 wrist fractures remained for assessment. 52 of them (with 54 fractures) received vitamin C, and 63 (with 65 fractures) placebo (figure).

There were no significant differences between the groups in terms of sex: 12 (22%) of fractures in the vitamin C group and 13 (20%) in the placebo group were in male patients. In the vitamin C group, age was in the range 27–88 (mean 57) years. In the placebo group the age range was 24–85 (60) years. Of all patients just five took vitamin supplements. Two of these (one in the vitamin C group and one in the placebo group) used a multivitamin preparation containing 50 mg vitamin C. Since this represented just one tenth of the trial dose and is the equivalent of a normal dietary intake, it was no reason for exclusion. Three other patients used a monovitamin preparation, namely vitamin A, B1, or B12, which also did not exclude them from the trial.

There was no significant difference between the groups with respect to side of the fracture, dominance, fracture type, or reduction (table 1).

RSD occurred in four (7%) fractures in the vitamin C group and 14 (22%) in the placebo group (95% CI for differences 2–26).

	Vitamin C	Placebo
Fractures	54	65
Side of fracture		
Right	27 (50%)	28 (43%)
Left	27 (50%)	37 (57%)
Dominance		
Yes	26 (48%)	32 (49%)
No	28 (52%)	33 (51%)
Fracture type		
23-A	31 (57%)	44 (68%)
23-B	14 (26%)	14 (21%)
23-C	9 (17%)	7 (11%)
Reduction	30 (56%)	40 (62%)

Table 1: **Baseline characteristics of fractures**

Characteristic	RSD (n=18)	No RSD (n=101)	Relative risk (95% CI)
Sex			0·22 (0·03–1·58)
Male	1 (6%)	24 (24%)	
Female	17 (94%)	77 (76%)	
Side of fracture			0·74 (0·31–1·78)
Right	7 (39%)	48 (47·5%)	
Left	11 (61%)	53 (52·5%)	
Dominance			1·31 (0·56–3·10)
Yes	10 (56%)	48 (47·5%)	
No	8 (44%)	53 (52·5%)	
Fracture type			0·37 (0·16–0·89)
23-A	7 (39%)	68 (67%)	
23-B+C	11 (61%)	33 (33%)	
Reduction	11 (61%)	59 (58%)	1·10 (0·46–2·64)
Complaints in plaster	12 (67%)	18 (18%)	0·17 (0·07–0·41)
Therapy			2·91 (1·02–8·32)
Vitamin C	4 (22%)	50 (50%)	
Placebo	14 (78%)	51 (50%)	

Table 2: **Relative risk of RSD according to characteristics of fractures**

	Odds ratio (95% CI)	p
Fracture type	0·09 (0·02–0·46)	0·0037
Complaints in plaster	0·1 (0·03–0·34)	0·0002
Therapy	4·22 (1·05–16·99)	0·0429

Table 3: **Logistic-regression analysis**

The four patients in the vitamin C group who developed RSD were all female. In the placebo group were 14 patients with RSD, of whom 13 were female and one male. The risk difference for women and men for RSD is 20% (5·4–34·1) and 8% (−7·0 to 22·2) respectively.

One patient in the placebo group had fractures on both sides, for which she had to undergo reduction On her dominant right-hand side she had a fracture type AO 23-B2.3 and on the left an AO 23-A2.2 fracture. Both reductions were satisfactory. This patient developed RSD on the right side.

Another patient in the placebo group had a simple AO 23-A2.1 fracture on her dominant left-hand side. She still had RSD due to an AO 23-C2.1 fracture on the right side, sustained 16 months previously. 8 weeks after the second wrist fracture on the left, she developed RSD there too.

RSD occurred significantly more often in older patients (p=0·008). The mean age was 64·5 years (SD 8·1) for patients with RSD and 57·7 years (SD 14·8) for those without RSD.

There was no association (table 2) between the occurrence of RSD and the side of the fracture or dominance.

There was a significant increase (0·37, 0·16–0·89) of RSD in type B and C fractures (AO classification).

No relation was found between the occurrence of RSD and the need to undergo reduction. Early complaints while wearing the plaster case are highly predictive of the occurrence of RSD (0·17, 0·07–0·41).

In the logistic-regression analysis of the predictive factors, fracture type, complaints in plaster, and vitamin C therapy had significant odds ratios. In this model age was not found to be a predictive factor despite the higher mean age in the RSD group (table 3).

Discussion

This study shows that the administration of vitamin C in patients with a wrist fracture was associated with a lower frequency of RSD. Although 17 of the 18 patients with RSD were women, sex was not a significant factor in the occurrence of RSD in this study. The mean age of the female participants was such that most women, and all women developing RSD, were postmenopausal. In our protocol we did not assess the oestrogen status of the female participants, but none was receiving oestrogen-replacement therapy. There is a possibility that oestrogen status is a confounding factor in relation to an inflammatory response contributing to the pathogenesis of RSD, but we found no evidence in this direction.

The frequency of RSD in our placebo group is high (22%), but not uncommon. Atkins and colleagues did two studies and showed frequencies of RSD after Colles' fracture of 25%[23] and even 37%.[24] Our study provides no explanation of the pharmacodynamic mechanism, nor the scavenger theory, but Zuurmond and colleagues[25] reported a healing effect in a limb with RSD by the application of local treatment with the free-radical scavenger dimethylsulphoxide.

In an experimental model Van der Laan and colleagues[5] induced free-radical-related soft-tissue damage by infusion with tert-butylhydroperoxide, resulting in increasing vascular permeability in skeletal muscle and necrosis of one hind limb of rats. Scintigraphy of RSD patients, with indium-111-labelled human non-specific polyclonal IgG, showed that increased vascular permeability for macromolecules, an important characteristic for inflammation, has a role in the development of RSD.[6]

Histological abnormalities in muscle specimens were seen in legs amputated as a result of RSD, by means of light and electronic microscopic analysis of skeletal muscle tissue and peripheral nerves.[18] However, there was no consistent abnormality of these peripheral nerves. The muscle fibres contained an increased amount of lipofuscin, which is unspecific but results from oxidation of unsaturated membrane lipids by free radicals and increases with age. Other morphological changes were a decreased number of type-I fibres, atrophic fibres, and capillary changes varying from thickened basal membrane to necrosis. All these changes seem to be related to ischaemic conditions and suggest involvement of microangiopathy. Van der Laan and colleagues[18] hypothesise that oxygen-derived free radicals are involved in the pathophysiology of RSD.

The histopathological findings and abnormalities in the tissues[5,18,26] cannot be explained just by disuse and psychological factors or constitution.[27] Therefore we support the theory that oxygen-derived free radicals are involved in the pathophysiology of RSD or complex regional-pain syndrome type I. The relation we noted between the occurrence of RSD and complaints while wearing the plaster cast has been described earlier by Field and colleagues.[28]

We found another predictive factor for the occurrence of RSD in a wrist fracture, namely fracture type (which is indirectly related to age). The incidence of RSD increased with comminution (and therefore severity) of the fracture, although Atkins and colleagues[24] found no such relation. We could find no relation between the occurrence of RSD and side of the fracture, dominant side, or reduction. None of the five patients who were taking vitamin supplements developed RSD.

In conclusion, vitamin C appears to be effective in prevention of reflex sympathetic dystrophy after wrist fractures. We suggest that this simple and cheap means of

prevention could also be useful in the prophylaxis of RSD after other injuries, such as trauma of the foot or ankle, talar and calcaneal fractures, or crural fractures. Further investigations are needed into the mechanism, dosage, and use of vitamin C in relation to the prevention and therapy of RSD in other lesions.

Contributors

Paul Zollinger was the principal investigator and wrote the protocol and the paper. Wim Tuinebreijer did data interpretation and statistical analysis. Robert Kreis contributed to the design of the trial. Roelf Breederveld was involved in data interpretation and protocol compliance. All investigators were involved in the design of the study and the preparation of the paper.

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