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Effect of vitamin C on prevention of complex regional pain syndrome type I in foot and ankle surgery

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ABSTRACT

Background: The public health cost impact of complex regional pain syndrome type I (CRPS I) is considerable in both emergency and scheduled orthopaedic surgery. We proposed to assess the effectiveness of vitamin C in prevention of CRPS I in foot and ankle surgery.
Methods: We carried out a "before–after" quasi-experimental study comparing two chronologically successive groups without (Group I: July 2002–June 2003) and with (Group II: July 2003–June 2004) preventive 1 g daily vitamin C treatment. All patients having surgery on the foot or ankle were enrolled, with the exception of diabetic foot cases. Several factors were analysed: sex, age, type of pathology, history of CRPS I, psychological context, tourniquet time, and cast immobilisation time.
Results: 420 feet (392 patients) were included in the study: 185 in Group I, 235 in Group II. CRPS I occurred in 18 cases in Group I (9.6%) and 4 cases in Group II (1.7%) ($p < 10^{-4}$), with history of CRPS I as a significantly correlated factor (relative risk = 10.4). The psychological context (anxio-depressive state) showed a (sub-significant) tendency to increase the risk of CRPS I (relative risk = 2.6).
Conclusion: Vitamin C has been shown to be effective in preventing CRPS I secondary to wrist fracture, but few data are available with respect to foot and ankle cases. The present study demonstrates the effectiveness of vitamin C in preventing CRPS I of the foot and ankle—a frequent complication in our control group (9.6%). The authors recommend preventive management by vitamin C.
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1. Introduction

The physiopathology of reflex sympathetic dystrophy syndrome (which is now called complex regional pain syndrome type I (CRPS I) according to the International Association for the study of Pain (IAPS) [1]) remains unclear, causing numerous uncertainties for diagnosis and treatment. Indeed, even the terminology was a subject of disagreement, being called reflex sympathetic dystrophy, algodystrophy or neurotrophic rheumatism; the term complex regional pain syndrome type I has now come to be generally accepted. The syndrome combines joint pain, trophic disturbance, bone demineralisation and a theoretical regressive evolution without sequelae. Clinically, it comprises two phases: a "hot" phase of circulatory disturbance, associated with pain and functional impairment; and a "cold" phase of trophic alteration, stiffness and tendon retraction. There is a great public health impact, notably in terms of sick leave, especially as the condition may persist for many weeks.

In 1999, Zollinger, in a prospective randomised study, showed vitamin C to be effective in preventing CRPS I following distal radius fracture [2].

We here report the results of a prospective study to assess the potential role of vitamin C in preventing CRPS I in scheduled foot and ankle surgery.

2. Materials ands methods

2.1. Study design

We carried out a "before–after" quasi-experimental study [3] comparing two chronologically successive groups without (Group I) and with (Group II) prophylactic vitamin C treatment. This was decided so as to avoid loss of recruitment with a strictly randomised protocol with a full patient-information file for written consent, approved by an ethics committee. It was prospective and with blinded statistical analysis until the end of the two part study period.

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2.2. Inclusion criteria

All patients having surgery from July 2002 to July 2004, for scheduled foot and ankle surgery by a single senior foot-and-ankle surgeon (JLB) with 15 years experience, were included.

From July 2002 to June 2003 (Group I) the patients had surgery without vitamin C, and from July 2003 to June 2004 (Group II) received preventive vitamin C treatment: 1 g on the first post-operative day, and then each morning for 45 days. This dosage and treatment duration were chosen in line with the only two publications available in the literature [2,4]. Compliance was checked at the post-operative consultations at 3 weeks and 3 months. In case of non-compliance, patients were excluded from analysis.

Surgical procedure and post-operative care did not change between these two periods.

2.3. Exclusion criteria

Diabetic patients were excluded. These patients' pain status is hard to estimate, in view of the associated lower-limb neuropathy. Any patient whose pathology did not concern the foot or ankle was excluded.

2.4. Methodology

Data were harvested from medical records and surgical reports.

Several parameters were noted and analysed: age, sex, history of CRPS I, psychological context of anxio-depression (either present or history of depression, current antidepressant/anxiolytic treatment, or severe anxiety state reported on pre-operative consultation), type of presenting pathology, type of anaesthesia, surgical procedure, tourniquet time, post-operative cast, and non-weight-bearing time.

Patients had radio-clinical follow-up on the 10th, 21st and 45th day post-operatively, and then every 3 months. All patients were followed up by the same physician (JLB).

The diagnosis of CRPS I was made from clinical data as proposed by the IASP criteria [5]. Two categories of classical reflex sympathetic dystrophy signs were distinguished, and diagnosis was made in the presence of the set A criterion or at least two set B criteria (Table 1). Bone pain remote from the operative locus (anterior dorsal part of the midtibial crest, metatarsal heads) assessed by comparison of pain on pressure between the two limbs (set A criterion) was used in a randomised study of algodystrophy treatments [6].

A descriptive univariate analysis was made of the study population and of the various parameters. Student's *t*-tests were applied to quantitative variables (after checking the Gaussian form of the distribution and the equality of the squares of the variance), or else the non-parametric Mann–Whitney test, and Pearson's χ^2 or Fischer's exact were used for categoric variables. Quantitative variables were compared by analysis of variance (ANOVA). Logistic regression multivariate analysis, assessing the association between a dependent variable and putative explanatory factors, was used to specify the relative risk of potential risk factors and take account of confusion factors. Individual data were processed using SPSS version 11.0 software for Windows [7].

Table 1
CRPS I criteria.

Set A criterion	Set B criteria
Persistent bone pain remote from the operative locus, assessed by pressure comparatively between the two limbs (dorsal part of anterior midtibial crest, and metatarsal heads)	Persistent nocturnal pain, causing insomnia
	Persistent locoregional inflammatory signs
	Suggestive radiological signs (demineralisation, spotty osteoporosis)

3. Results

3.1. Patients included

Four hundred and twenty feet (392 patients) were included.

Group I without vitamin C, having surgery from July 2002 to June 2003, comprised 185 feet: 177 patients (44 males, 133 females). Mean age at time of surgery was 47.1 ± 17 years; range, 16–78 years.

Group II receiving prophylactic vitamin C treatment, having surgery on between July 2003 and June 2004, comprised 235 feet: 215 patients (49 males, 166 females). Mean age at time of surgery was 51 ± 16 years; range, 15–87 years.

There were no significant inter-group differences on general characteristics (Table 2).

3.2. Effect of vitamin C

CRPS I occurred in 9.6% of Group I patients ($n = 18$), as against 1.7% ($n = 4$) in Group II ($p < 0.0001$). One Group II patient stopped vitamin C after 1 day's treatment, and went on to develop post-operative CRPS I; he was excluded from analysis.

3.3. Associated factors

36.3% of patients presenting CRPS I presented a psychological context suggestive of an anxio-depressive state, compared to 14.3% of patients free of CRPS I ($p < 0.001$). 31.8% of patients presenting CRPS I had had a history of the syndrome, as against 3.2% of those unaffected post-operatively ($p < 0.0001$).

No correlations emerged between CRPS I on the one hand and age, sex, tourniquet time, cast fitting, immobilisation time, type of pathology, or type of surgical protocol on the other. The pathologies being operated on were broadly similar between the two groups (Table 3).

Logistic regression analysis disclosed significant odds ratios for prophylactic vitamin C treatment and for history of CRPS I. The risk of presenting reflex sympathetic dystrophy was five times lower in patients receiving vitamin C and ten times greater in those with a

Table 2
Main characteristics in the two groups.

	Group 1	Group 2	*p*-Value
Side			
Right	101 (54.6%)	110 (46.8%)	ns
Left	84 (45.4%)	125 (53.2%)	
History of CRPS I			
No	173 (93.5%)	227 (96.6%)	ns
Yes	12 (6.5%)	8 (3.4%)	
Anaesthesia			
General	117 (63.2%)	127 (54%)	ns
Spinal	43 (23.3%)	60 (25.5%)	
Popliteal blockade	25 (13.5%)	48 (20.5%)	
Psychological context			
No	152 (82.2%)	203 (86.4%)	ns
yes	33 (17.8%)	32 (13.6%)	
Age	47.1 years	51 years	ns
Sex (M/F)	48/137	55/180	ns
Mean tourniquet time	54.5 min	47.3 min	ns
Mean non-weight-bearing time	36.7 days	30.7 days	ns

Table 3
Type of pathology presenting in the two groups.

	Group 1	Group 2	*p*-Value
Forefoot (M1 Scarf, MTP1 arthrodesis, Weil osteotomies, M5 Scarf, claw toe correction)	116 (62.7%)	153 (65.1%)	ns
Hindfoot (arthrodesis—osteotomy)	7 (3.8%)	9 (3.8%)	ns
Ankle bone (T.A.R—ankle arthrodesis)	9 (4.9%)	21 (8.9%)	ns
Ankle tendon (ankle ligament reconstruction—Achilles surgery)	36 (19.5%)	32 (13.6%)	ns
Neurological	5 (2.7%)	4 (1.7%)	ns
Simple hardware removal	11 (5.9%)	13 (5.5%)	ns
Other	1 (0.5%)	3 (1.3%)	ns

history of reflex sympathetic dystrophy. Logistic regression failed to reveal psychological context as a significant predictive factor, the twofold greater occurrence of reflex sympathetic dystrophy in subjects presenting an anxio-depressive state just failing to reach the significance threshold (Table 4).

4. Discussion

Our quasi-experimental study showed a 9.6% incidence of reflex sympathetic dystrophy in the control group without preventive vitamin C treatment, versus 1.7% in the experimental subjects. The relative risk of developing CRPS I was reduced fivefold in patients treated prophylactically with vitamin C.

Reflex sympathetic dystrophy continues to feature as a frequent post-operative complication. The actual incidence appears variable (10.5–37%), and has mainly been assessed in the context of wrist fracture [8–11]. There is little literature for the incidence of this syndrome in foot and ankle surgery: Riou et al. [12], in a prospective randomised study of prevention by thyrocalcitonin, reported 13.6% incidence of CRPS I for foot surgery (hallux valgus, fractures, arthrodesis). The present series has the particularity of concerning scheduled surgery, with the CRPS I occurring secondarily to the operation rather than to trauma. In the wrist fracture literature, the CRPS I was post-traumatic, and not always associated with surgery at all. Cazeneuve et al. [4] in 2002 reported a 10% incidence of CRPS I in his surgically managed control group (not receiving vitamin C), and Zollinger et al. [2] in 1999 reported a 22% rate in his orthopaedically managed control group (likewise, not receiving vitamin C). In the experimental groups, receiving vitamin C, Zollinger reported a 7% incidence of reflex sympathetic dystrophy (relative risk: 0.17) and Cazeneuve 2.1%.

Another factor was found to be significantly associated with the occurrence of CRPS I in our series: for patients having a history of the syndrome, the risk was increased 10-fold. 31.8% of patients developing post-operative CRPS I had already suffered from it in the past.

There was a clear trend with respect to the psychological context, the relative risk increasing twofold in case of an anxio-depressive state, although this difference failed to attain significance ($p = 0.06$). Psychological factors have often been pointed to, but without statistical proof. It is, indeed, not easy to determine a patient's psychological context, and attributing an anxio-depressive state is subjective and examiner-dependent.

Table 4
Logistic regression analysis.

	Relative risk	*p*-Value	Confidence interval
Vitamin C	0.197	0.005	0.063–0.611
History of CRPS I	10.449	0.000	3.369–32.408
Psychological context	2.580	0.065	0.944–7.055

Although 17 of the 22 patients who developed CRPS I in our series were women, sex did not appear to correlate with the risk. Time in cast, surgical protocol and type of pathology also showed no correlation with the occurrence of CRPS I. Twenty two patients in all developed post-operative CRPS I. Although the total study population comprised 420 patients, the incidence of CRPS I was slight, making the use of logistic regression criticisable and accounting for the wide confidence intervals on the odds ratios.

We drew up a diagnostic check-list so as best to limit biased attributions of post-operative CRPS I. There is, however, no sensitive and specific criterion for the syndrome, and diagnosis is founded on a cluster of arguments [13]. Holder et al. [14] proposed the following criteria for the foot: diffuse pain, vasomotor disturbance, and a positive lumbar sympathetic nerve blockade response. Scintigraphy revealed diffuse hyperfixation, with 100% sensitivity, 80% specificity, and a rather low positive predictive value of 54%. Colton and Fallat [15] proposed lumbar sympathetic nerve blockade as a diagnostic test and treatment for reflex sympathetic dystrophy. Harris et al. [16] reported the following sensitive signs of CRPS I: burning pain, allodynia, cutaneous hyperaesthesia, and local erythema. The major sign seemed to us to be the occurrence of persistent bone pain on pressure remote from the operative locus (anterior dorsal part of the midtibial crest, metatarsal heads) and was a sufficient diagnostic sign; some authors [6,17] had proposed measuring the pressure tolerance threshold with a dolorimeter to compare bone pain on pressure between the two legs and feet. The frequent occurrence of post-operative oedema in foot and ankle surgery cannot count as a determining argument. Radiological signs, when available, were usually found late on in clinical management, and were classified as secondary. We resorted to scintigraphy only in one doubtful case.

Several factors have been proposed to account for CRPS I: exaggerated inflammatory and neuroendocrine response, sympathetic nervous system anomaly, or central or peripheral nervous system dysfunction. The pathology appears more complex. Raja and Grabow [18] highlighted the psychological factors that seem to promote CRPS I. Physiopathological studies showed free radicals hindering microcirculation [10–21]. Van der Laan et al. [22] found muscle fibre alteration in CRPS I, causing lipid membrane oxidation by free radicals, leading to capillary alterations which might mean that microangiopathy is at work in the physiopathology of the syndrome. Vitamin C is a natural anti-oxidant, blocking free radicals and thereby protecting the capillary endothelium [23]. Vitamin C's antioxidant action has been tested in animals, demonstrating its role in preventing capillary leakage and in neutralising free radicals [21].

Vitamin C appears effective in preventing post-operative CRPS I. Although generally post-traumatic, CRPS I also occurs in scheduled surgery. Vitamin C seems to us to offer a simple and cost-effective means of limiting this complication. Our results need confirming in a prospective study involving both upper and lower-limb affections.

Furthermore, the dose of vitamin C in the literature has varied: from 500 mg for Zollinger et al. [2] to 1 g for Cazeneuve et al. [4], and the sufficient effective dose needs determining. Recently, however, in 2007, in a second randomised study [24] comparing the prevention effect of three vitamin C doses (200–500–1500 mg) in wrist fractures, Zollinger found a prevalence of CRPS I of 10.1% in his placebo group, 4.2% in the 200-mg group, 1.8% in the 500-mg group and 1.7% in the 1500-mg group, and concluded that a daily dose of 500 mg for 50 days is to be recommended.

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