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Original article

Efficacy of vitamin C in preventing complex regional pain syndrome after wrist fracture: A systematic review and meta-analysis

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ABSTRACT

Background: Complex regional pain syndrome type I (CRPS-I), previously known as reflex sympathetic dystrophy, is common after conservatively or surgically treated wrist fractures. Several studies support the efficacy of vitamin C in preventing CRPS-I, although the data are somewhat conflicting. The primary objective of this systematic literature review and meta-analysis was to assess the efficacy of vitamin C therapy in preventing CRPS-I after a wrist fracture.
Methods: Randomised, placebo-controlled trials of vitamin C to prevent CRPS-I after wrist fractures were sought in the three main databases: PubMed (1980 to December 2015), CENTRAL (Central 2015, number 12), and Embase (1980 to December 2015). Two authors worked independently to select articles. Data from selected articles were collected independently.
Results: Three randomised placebo-controlled trials in a total of 875 patients were included. Treatment was non-operative in 758/890 (85.1%) fractures and operative in 132 (14.9%) fractures. Vitamin C supplementation was started on the day of the injury and continued for 50 days. In the group given 500 mg of vitamin C daily, the risk ratio for CRPS-I was 0.54 (95%CI, 0.33–0.91; $P = 0.02$). Thus, the risk of developing CRPS-I was significantly decreased by prophylactic treatment with 500 mg of vitamin C per day. The heterogeneity rate was 65% (non-significant).
Conclusion: Daily supplementation with 500 mg of vitamin C per day for 50 days decreases the 1-year risk of CRPS-I after wrist fracture.
Level of evidence: II, systematic review of level I and II studies.

1. Introduction

Complex regional pain syndrome type I (CRPS-I), previously known as reflex sympathetic dystrophy, is a common complication of conservatively or surgically treated wrist fractures [1,2]. The development of CRPS-I considerably lengthens the time to recovery after a traumatic injury [3] and therefore has a severe impact on work, social activities, and psychological well-being [4]. CRPS-I should be distinguished from CRPS type II, previously called causalgia, in which the symptoms are due to nerve damage. CRPS-I, in contrast, is an exaggerated inflammatory response to a traumatic injury, due to over activity of the sympathetic nervous system and manifesting as oedema, pain, and motion range limitation [1,5]. Whereas the diagnosis is readily established, the management is challenging. No effective curative treatment is available. Symptomatic measures and psychological support are the only therapeutic options. Devising effective preventive strategies is consequently a key priority.

Vitamin C is a well-documented anti-oxidant capable of stabilising reactive oxygen species (ROS), which cause damage to membrane lipids and to the microcirculation [6–8]. In patients with burn injuries, high-dose vitamin C supplementation decreases vascular permeability, thereby limiting protein losses. Vitamin C diminishes lipid peroxidation, the process by which ROSs damage the vascular endothelial cells [9]. The post-burn increase in vascular permeability is a consequence of endothelial barrier damage by ROSs. The endothelial barrier is also impaired in CRPS-I. Burn injuries and CRPS-I share similarities, as both involve inflammation and micro-angiopathy.

In several studies, vitamin C supplementation demonstrated efficacy in preventing CRPS-I, although the results were conflicting. A recent meta-analysis suggested benefits of vitamin C supplementation in avoiding CRPS-I after traumatic injury to the lower limb [10]. No similar studies are available for the upper limb.

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The primary objective of this systematic literature review and meta-analysis was to assess the efficacy of vitamin C supplementation in preventing CRPS-I after wrist fractures.

2. Materiel and methods

This work was conducted and reported in compliance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [11].

2.1. Research strategy

The search was conducted in three databases: MEDLINE via PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL 2015, number 12), and Embase. The search terms referred to the trial intervention ('ascorbic acid', 'vitamin C'), population ('wrist fracture'), and complication of interest ('complex regional pain syndrome', 'reflex sympathetic dystrophy', 'algoneurodystrophy', 'chronic pain'). A search algorithm was developed for each database. No time limits were set. The reference list of each article or report identified by the search and any previously published meta-analyses on the topic of interest were examined. Finally, ongoing trials were identified by searching ClinicalTrials.gov. The last search was performed on 15 December 2015.

2.2. Study selection criteria and modalities

We included randomised placebo-controlled trials of the efficacy of vitamin C supplementation in preventing CRPS-I after a wrist fracture, in any language, whether the report was published, unpublished, or in press. Neither systematic reviews nor reports of expert opinion were included. Relevant trials were selected by two of us (F.A. and A.F.), who worked independently from each other and resolved disagreements by consensus. Excluded trials were listed, with the reasons for exclusion.

2.3. Study quality assessment

The risk of bias in the included studies was evaluated using the Cochrane Risk of Bias Tool (selection bias, attrition bias, detection bias, and performance bias) applied independently by two of us (F.A. and A.S.). These criteria served to determine whether the level of potential bias was high or low for each of the following components: random sequence generation, allocation concealment, double-blinding, selective data reporting, and missing data.

2.4. Extraction and review of the data

Data in the included studies were extracted to standardized forms by two evaluators (F.A. and A.S.), who worked independently from each other. The following were collected: publication date, journal, country, patient demographics (age, gender, side fractured, and type of fracture), treatment of the fracture (surgery and duration of immobilisation), dose and duration of supplemental vitamin C, and clinical outcomes (development of CRPS-I).

The primary outcome measure was the proportion of patients with CRPS-I within 1 year after the injury.

2.5. Statistical analyses

The data were analysed using RevMan 5 software (Review Manager, The Cochrane Collaboration 2011). Heterogeneity of the included studies was evaluated by determining the I^2 statistic. I^2 values were interpreted as follows: 25–49%, low heterogeneity; 50–74%, moderate heterogeneity; and >75%, high heterogeneity. Relative risks (RRs) with their 95% confidence intervals (95%CIs) were computed using a fixed-effects model when heterogeneity was non-significant and a random-effects model otherwise. A funnel plot was built to assess publication bias.

Descriptive statistics were computed using GraphPad Prism version 6.04 for Windows (GraphPad Software, La Jolla, CA, USA) with P values ≤ 0.05 considered significant. Between-group comparisons were performed by applying the Chi^2 test for qualitative data and Student's test for quantitative data.

3. Results

3.1. Included studies

Of 860 randomised placebo-controlled trials identified by the literature search, 3 were included [12–14] (Fig. 1).

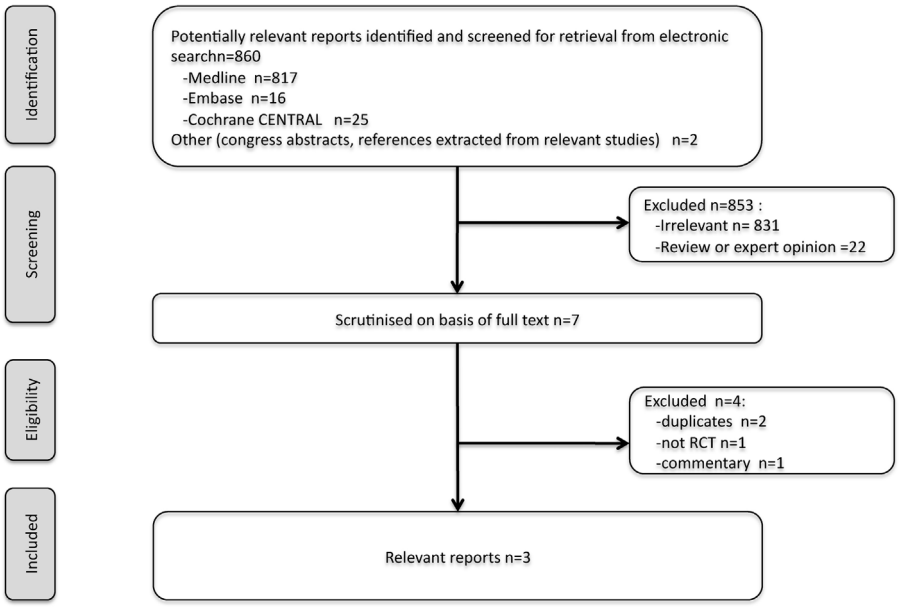

Fig. 1. PRISMA flow-chart of study selection.

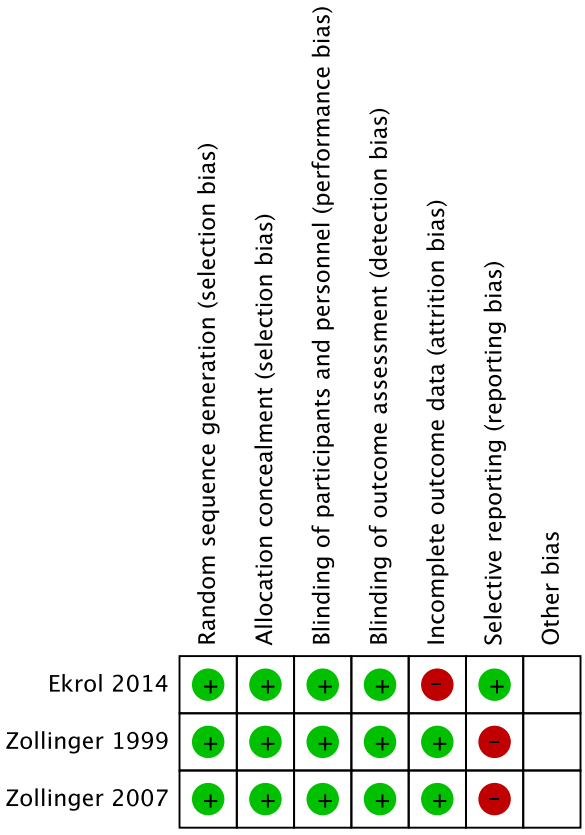

Fig. 2. Methodological quality of the included studies, with an evaluation of bias (+: low risk of bias; –: high risk of bias).

3.2. Characteristics and methodological quality of the included studies

All three studies were randomised placebo-controlled trials and had the occurrence of CRPS-I within the first year post-injury as the primary outcome. Fig. 2 reports the potential levels of bias, which were acceptable.

3.3. Patient characteristics

The three trials included a total of 875 patients (890 fractures), of whom 549 (62.5%) received vitamin C and 326 (37.5%) a placebo. There were 686 females and 189 males (female/male ratio, 0.3) with a mean age of 59.6 ± 3 years. The distribution of wrist fracture types according to the AO Foundation was as follows in the vitamin C group: type A (extra-articular), 301 (54.8%); types B and C (articular), 222 (40.2%); and unclassified, 28 (5%); in the placebo group, there were 166 (50.3%) type A fractures, 128 (38.6%) types B and C fractures, and 37 (11.1%) unclassified fractures. Thus, about half the patients in both groups had type A fractures.

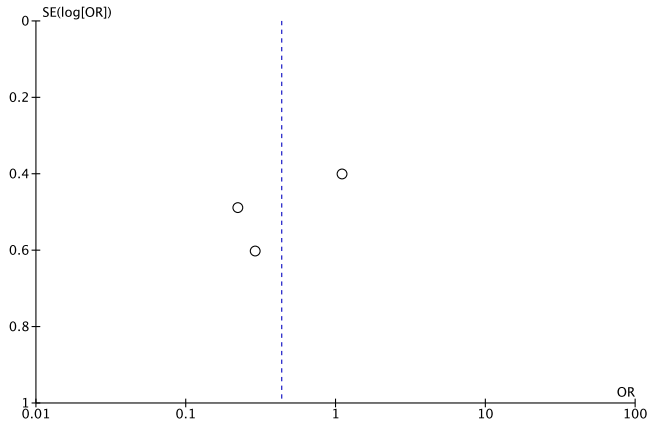

Fig. 4. Funnel plot to assess the risk of publication bias.

3.4. Treatment characteristics

Oral vitamin C supplementation was started on the day of the injury and continued for 50 days in all three studies. The daily dosage was 500 mg in two studies [13,14]. The remaining study evaluated three dosages: 200, 500, and 1500 mg [12].

The wrist fracture was treated non-operatively in 758 (85.1%) cases and operatively in 132 (14.9%) cases.

3.5. Description of the included studies (Tables 1 and 2)

The earliest of the three trials, by Zollinger et al., was reported in 1999 [13]. In this prospective double-blind trial, patients with distal radius fractures were allocated at random to oral vitamin C, 500 mg ($n = 52$) or a placebo ($n = 63$), daily for 50 days. All patients were treated conservatively, with immobilisation for 50 days; patients treated surgically were excluded. CRPS-I was significantly less common in the vitamin C group than in the placebo group (7% versus 22%; 95%CI for differences, 2–26). Other factors significantly associated with CRPS-I were articular as opposed to extra-articular fracture (odds ratio [OR], 0.09; 95%CI, 0.02–0.46) and pain while wearing the cast (OR, 0.15; 95%CI, 0.03–0.34).

In 2007, the same investigators reported another randomised controlled trial, in which 317 patients with wrist fractures treated conservatively or surgically were included at multiple centres [12]. The patients were allocated at random to vitamin C supplementation in a dose of 200, 500, or 1500 mg/day or to a placebo, taken orally for 50 days starting on the day of the injury. CRPS-I was significantly less common with vitamin C in any dose than with the placebo (2.4% versus 10%, $P = 0.002$). Separate analyses of the three vitamin C doses showed that only the 500 and 1500 mg doses significantly diminished the risk of CRPS-I ($P = 0.007$ and $P = 0.005$, respectively).

The third study, by Ekrol et al., is a double-blind, randomised, placebo-controlled evaluation of oral vitamin C, 500 mg/day, for 50 days starting on the day of the injury in 336 patients with

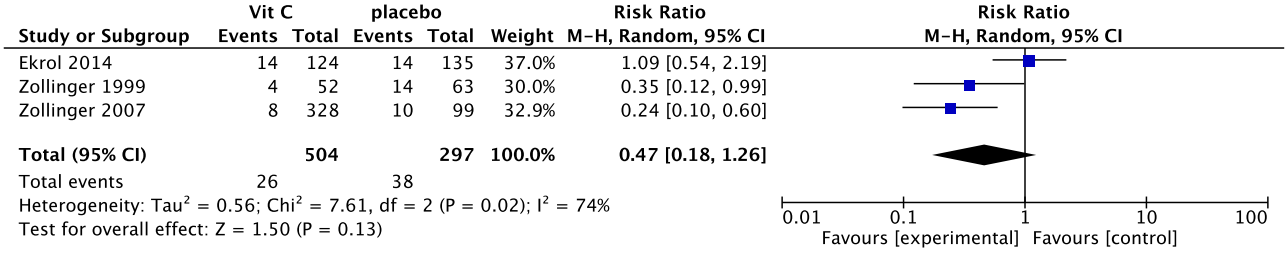

Fig. 3. Forest plot of the combined relative risk of CRPS-I by meta-analysis, with the 95% confidence interval, for all vitamin C doses pooled.

Table 1
Description of the included studies.

	Study design	Number of groups	Patients	Evaluation time points	Dose of vitamin C	Time of treatment initiation	Duration of treatment (days)	AO/OTA fracture type	Type of fracture management	Clinical criteria used to assess CRPS-I
Zollinger et al. 1999 [13]	RCT	2	Vitamin C group, $n = 52$ (11 M/41 F); mean age, 57 years Placebo group, $n = 63$ (13 M/50 F); mean age, 60 years	Days 7, 30, and 45 Months 4 and 6 1 year	500 mg	D0	50	Type A, $n = 75$ Type B, $n = 28$ Type C, $n = 16$	Non-operative, $n = 115$	Diffuse pain in the wrist Temperature difference vs. the other side Skin colour difference vs. the other side Diffuse oedema Motion range limitation Symptom exacerbation after activities
Zollinger et al. 2007 [12]	RCT	4	Vitamin C group, $n = 328$ (55 M/273, F); mean age, 62.7 years Placebo group, $n = 99$ (20 M/79 F); mean age, 61.4 years	1 year	200 mg ($n = 96$) 500 mg ($n = 114$) 1500 mg ($n = 118$)	D0	50	Type A, $n = 231$ Type B, $n = 90$ Type C, $n = 106$	Non-operative, $n = 291$ Surgical, $n = 37$	Diffuse pain in the wrist Temperature difference vs. the other side Skin colour difference vs. the other side Diffuse oedema Motion range limitation Symptom exacerbation after activities
Ekrol et al. 2014 [14]	RCT	4	Vitamin C group, $n = 169$ (44 M/125 F); mean age, 55 years Placebo group, $n = 167$ (46 M/121 F); mean age, 58 years	6 weeks 1 year	500 mg	D0	50	Type A, $n = 111$ Type B, $n = 33$ Type C, $n = 77$	Non-operative, $n = 252$ Surgical, $n = 84$	Score Atkins (> 3/5) Neuropathic pain Vasomotor instability or excessive sudation Oedema Motion range limitation Joint contractures

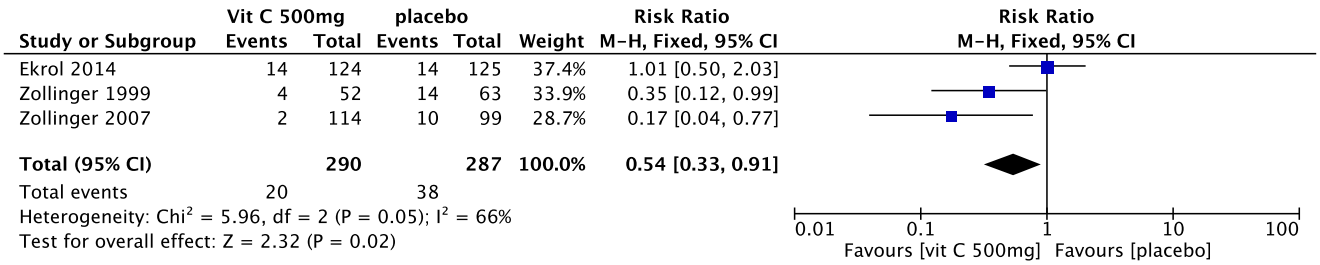

Fig. 5. Subgroup analysis: forest plot of the combined relative risk of CRPS-I by meta-analysis, with the 95% confidence interval, for the 500-mg vitamin C dose.

Table 2
Evaluation of the frequency of complex regional pain syndrome type I (CRPS-I).

Studies	1-year occurrence of CRPS-I, *n* (%)		
	Vitamin C	Placebo	*P* value
Zollinger et al. [13]	4 (7)	14 (22)	< 0.05
Zollinger et al. 2007 [12]	Any dosage: 8 (2.4)	10 (10.1)	0.002
	200 mg: 4 (4.2)		NS
	500 mg: 2 (1.8)		0.007
	1500 mg: 2 (1.7)		0.005
Ekrol et al. 2014 [14]	14 (8.2)	14 (8.3)	1

NS: non-significant.

wrist fractures [14]. After 6 weeks, patients in the vitamin C group with non-displaced fractures treated conservatively or surgically had a significantly higher frequency of CRPS-I compared to those in the placebo group ($P = 0.022$). No significant between-group differences were found in patients with displaced fractures. The frequency of CRPS-I at 1 year was similar in the two groups. Thus, vitamin C supplementation failed to diminish the risk of CRPS-I in this study. Patients with complex fractures and those managed with plate fixation were excluded from the study population.

No complications related to vitamin C supplementation were recorded in any of the three studies.

3.6. Meta-analysis of the efficacy of vitamin C in preventing CRPS-I

By meta-analysis, the relative risk (RR) of CRPS-I after a wrist fracture was not significantly diminished in the group given vitamin C in any dose (200, 500, or 1500 mg) (RR, 0.55; 95%CI, 0.34–0.87; $P = 0.13$). Heterogeneity was high (74%) and statistically significant (Figs. 3 and 4).

When the analysis was confined to the 500-mg vitamin C dosage versus placebo, the RR of CRPS-I was 0.54 (95%CI, 0.33–0.91; $P = 0.02$). Thus, the risk of CRPS-I was significantly decreased by vitamin C in the 500-mg dosage. The heterogeneity rate was 65% and non-significant (Fig. 5).

4. Discussion

This study is the first meta-analysis in which the efficacy of vitamin C supplementation in preventing CRPS-I was assessed only in patients with wrist fractures. The results showed that vitamin D supplementation in a daily dosage of 500 mg for 50 days halved the risk of CRPS-I within the first year after a wrist fracture.

As established by the 2007 trials assessing multiple doses, a dosage of at least 500 mg is required. Lower dosages were not effective. This dose-dependency explains that the meta-analysis comparing vitamin C in any dose to a placebo showed no significant preventive effect.

Vitamin C supplementation has been proven to exert a number of therapeutic effects. In burn patients, vitamin C minimises the oedema by decreasing the exaggerated vascular permeability. Vitamin C is a powerful ROS neutraliser. Beneficial effects on fracture healing have been reported, suggesting potential usefulness in trauma patients [15,16]. However, the risk of adverse effects should be assessed. Vitamin C supplementation is safe in healthy individuals but may induce complications (fatigue and lethargy) when used in high dosages (28 g/day) [17]. None of the studies included in the present literature review reported complications with vitamin C supplementation in a daily dosage of 500 mg.

No consensus exists about the definition of CRPS-I, which may therefore vary across groups of investigators. The diagnosis of CRPS-I relied solely on clinical findings in published studies. Zollinger et al. applied the following diagnostic criteria described by Veldman et al. [18]: diffuse pain in the wrist, temperature difference compared to the other side, skin colour difference compared to the other side, diffuse oedema, motion range limitation, and symptom exacerbation by activity. Ekrol et al. used the criteria developed by Atkins (neuropathic pain, vasomotor instability or excessive sweating, oedema, motion range limitation, and joint contractures) [1,18]. However, both criteria sets include oedema, pain, and motion range limitation.

The limitations of this meta-analysis are related to the small number of included studies. Only randomised placebo-controlled trials were considered, in order to obtain a high level of evidence and, therefore, a high-grade recommendation. The report by Ekrol et al. [14] does not indicate the proportions of patients treated conservatively and surgically in each group. Consequently, a comparison of vitamin C effects between these two treatment strategies was not feasible. Furthermore, the reporting of two studies by the same group at an interval of a few years may have resulted in publication bias. Nevertheless, no overlap occurred between the two patient cohorts, and both studies were of high methodological quality. Furthermore, the funnel plot showed no evidence of publication bias.

5. Conclusion

Vitamin C supplementation in a daily dosage of 500 mg for 50 days may halve the risk of CRPS-I within the first year after a wrist fracture and is therefore recommended. Further double-blind randomised placebo-controlled trials are needed to further support this recommendation.

Disclosure of interest

P. Hardy is a consultant for Arthrex and Zimmer. T. Bauer is a consultant for Arthrex.

The other authors declare that they have no competing interest.

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