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FAST TRACK

**Vitamin C 500 mg/d
for 7 weeks
is worth
recommending
to prevent
complex regional
pain syndrome
after fracture**

PURLs methodology

This study was selected and evaluated using FPIN's Priority Updates from the Research Literature (PURL) Surveillance System methodology. The criteria and findings leading to the selection of this study as a PURL can be accessed at www.jfponline.com/purls.

Give vitamin C to avert lingering pain after fracture

Practice changer

Vitamin C 500 mg daily for 50 days reduced the risk of complex regional pain syndrome for patients with a wrist fracture.

We think vitamin C 500 mg a day for 7 weeks is well worth recommending.¹

Strength of recommendation

A: Based on 2 consistent, well-designed randomized controlled trials (RCTs)

Zollinger PE, Tuinebreijer WE, Breederveld RS, Kreis RW. Can vitamin C prevent complex regional pain syndrome in patients with wrist fractures? A randomized, controlled, multicenter dose-response study. *J Bone Joint Surg Am* 2007; 89:1424-1431.¹

ILLUSTRATIVE CASE

Your patient is an 83-year-old woman who fell at home. Radiographs show a distal radial fracture, which is treated with casting. You know that a quarter of patients with wrist fractures will suffer from complex regional pain syndrome, and there is no well-established treatment for it. Is there any way to reduce this woman's chance of getting this painful syndrome?

BACKGROUND

■ Often misdiagnosed

We were surprised to learn how commonly patients suffer from complex regional pain syndrome (CRPS) after a fracture.

We think this diagnosis is frequently missed or misdiagnosed. Even with resolution, however, symptoms can be bothersome—and in 1% to 2% of cases, quite severe.

CRPS, a syndrome of pain and autonomic dysfunction after trauma, is divided into 2 types:

- type I has no obvious damage to nerves
- type II is due to definite damage to nerves (causalgia).

The etiology of CRPS (all further references here will be to type I) is still unclear, but not for lack of proposed theories. Sigmund Freud suggested that it has an origin in personality; there is little evidence to support his theory.²

Other theories include microtrauma to nerves, sympathetic nervous system abnormalities (hence the former name, reflex sympathetic dystrophy), abnormalities of the inflammatory response, and physiologic responses to immobilization. It is often described as a biphasic syndrome, with early edema followed by contracture and stiffness. It typically affects the extremities.²

CRPS more likely in women. A population-based study in Olmsted County, MN found an incidence of 5.5 per 100,000 person-years, with a prevalence of 20.6 per 100,000. Women were affected 4 times more than men.³ Fracture (46%) and sprain (12%) were the leading triggers, followed by other injuries, including crush, stroke, and contusion.

“My patients saw me, but I didn’t see them”

Apparently quite a few patients with complex regional pain syndrome (CRPS) saw me during my 20 years of practice, but I did not see them, or at least I did not recognize their symptoms.

As many as 50% of cast complaints—or post-cast complaints—probably represented CRPS. I wrote them off in all but the most severe cases, which were so dramatic they couldn’t be written off.

I vividly remember the suffering those patients experienced, as well as my feelings of helplessness to offer any relief. CRPS is still not

treatable, but now we know that vitamin C can help prevent it, or at least shorten its severity and duration. Granted, the symptoms can be mild, and most resolve spontaneously, but it can go on for months and it can be truly horrific in a small percent (1%–2%).

Here is an instance in which an ounce of prevention is worth more than a pound of cure.

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Over half of patients may suffer

Despite typically reported rates of 1% to 2% for severe, chronic CRPS following these injuries, it appears that milder cases are substantially more common.

In a cohort of 274 patients with Colles’s fractures, at 2 weeks, 24% met all 4 of the criteria used in the study to define CRPS, specifically:

- tenderness
- vascular instability
- stiffness
- objective swelling of areas distal to and distinctive from the fracture.

Although 48% met none of the criteria, the remaining 28% had at least some of the criteria.⁴

Most patients recover. Patients with partial CRPS improved more rapidly than those with CRPS; by 5 months, most had recovered completely. Patients with definitive CRPS also improved, although about 65% still reported stiffness in hands and wrists at 5 months. Another cohort study of 100 patients, also with Colles’s fractures, found similar rates of CRPS 9 weeks.⁵

CLINICAL CONTEXT

■ Treatments are not very effective

A systematic review of therapeutic options found 18 randomized controlled studies evaluating possible therapies for CRPS.⁶

The overall quality of data was low. The authors concluded there was little to no evidence for sympathetic blockade (either via stellate ganglion block or RIS block), radical scavenging with DMSO, prednisolone, acupuncture, or manual lymph drainage. Bisphosphonates and calcitonin, as well as *qigong* exercises, did show some potential, but data were too limited to draw a firm conclusion.

Guidelines recommend early intervention with physical and psychological therapy, as well as adequate pain control.⁷

The systematic review also identified 2 studies of preventive interventions. A pilot study of vitamin C (by the authors of the trial that is the subject of this PURL) showed some efficacy.⁸ An RCT of IV guanethidine found no benefit compared with saline.⁶

STUDY SUMMARY

■ Vitamin C reduced the rate of CRPS

This randomized, multicenter, dose-ranging, placebo-controlled trial was performed at 3 hospitals in the Netherlands.¹ Any adult (>18 years of age) with a fracture of one or both wrists treated in the emergency departments of these hospitals was invited to participate. During 2001–2004, there were 2137 patients with wrist fractures. Of these, 416 (19.5%) patients (with 427 fractures)

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“Granted, pain can be mild, but it can go on for months”

You can be a “REALITY CHECKER”

If you are in full-time clinical practice, a medical director of a practice, or otherwise directly involved in decision-making about adopting new practices, join our team of “reality checkers.”



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TABLE 1

Veldman's criteria for diagnosis of complex regional pain syndrome, type 1

Must have 4 of the 5 symptoms below, at the affected hand or wrist, or during activity with that wrist:

- Unexplained pain, not normal for typical treatment course
- Difference in skin color (compared to other wrist)
- Diffuse edema
- Difference in skin temperature (compared to other wrist)
- Limited range of motion, not normal for typical treatment course

were enrolled in the study. The study was double-blinded, and allocation was adequately concealed. There was 100% follow-up of all patients. Of enrolled patients, 82.4% were women, and the average age of all subjects was 62.4 years.

Patients were randomized into 1 of 4 groups: placebo, vitamin C 200 mg daily, vitamin C 500 mg daily, or vitamin C 1500 mg daily for 50 days. Other fracture therapy was undertaken at the discretion of the treating physician. Patients were evaluated at 1 week, 4 or 5 weeks (or cast removal), 6 or 7 weeks, 12 weeks, and 26 weeks. After 1 year, patients were contacted by phone or mail to confirm their status using Veldman's criteria (TABLE 1).⁸

10% of the placebo group had CRPS after 1 year

One year after the fracture, 10% of placebo patients had a diagnosis of CRPS. Rates of CRPS were 4%, 2%, and 2% in the 200 mg, 500 mg, 1500 mg daily dosing of vitamin C, respectively (TABLE 2).

There was no association between the development of CRPS and site of fracture, whether the fracture was displaced or intraarticular, or whether surgical therapy was chosen (although 90% of the fractures were treated with casting). Of note: all of the patients who developed CRPS were female; however, only 75 men were enrolled (18%).

Older patients were at increased risk, and patients with complaints about

their cast were substantially more likely to have CRPS (number needed to harm [NNH]=2.6; odds ratio [OR]=5.73; 95% confidence interval [CI], 2.11–15.57).

WHAT'S NEW?

Effective dose: 500 mg/d vitamin C for 50 days

Vitamin C at a dose of at least 500 mg/day for 50 days reduced the rate of CRPS from 10% to 2% (number needed to treat [NNT]=13). This is the second study undertaken by the same investigators to demonstrate risk reduction.⁸ The previous study enrolled only 129 patients, but found an absolute risk reduction of 15% (NNT=7; $P<.05$) for patients taking 500 mg of vitamin C.

Patients who complained about their casts were at substantially higher risk of being diagnosed with CRPS (OR=10.0; 95% CI, 2.9–33), suggesting that cast complaints may be a harbinger.

The more recent study was also designed to determine the effective dose for vitamin C. Doses of 200 mg daily reduced the risk, but the effect was not statistically significant. The effect size for the 500 mg and 1500 mg doses, on the other hand, were essentially identical, and both statistically and clinically significant.¹

CAVEATS

Selection bias?

The study enrolled less than 20% of potentially eligible patients, raising the possibility that only patients who might benefit from vitamin C prophylaxis were enrolled. However, almost two thirds of those eligible were either never approached due to the emergency department being busy (43%), or refused randomization (14%) after they were informed in the consent process that there was evidence of benefit of vitamin C, based on the prior trial.⁸ Therefore, selection bias seems an unlikely explanation for the positive results. This is the second trial to show the same finding, which is reassuring.

No men had CRPS in either group in this study, so there is no evidence to show

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Older patients are at greater risk for complex regional pain syndrome

whether or not this intervention works in men. We are unaware of any physiologic reason to suggest that vitamin C would have a differential effect in men. In the earlier study, only 1 man (in the placebo group) got CRPS, for an absolute risk difference of 0.08 (95% CI, -0.07 to 0.27).⁸

What are the diagnostic criteria?

There is no universal agreement on the diagnostic criteria for CRPS. This study used Veldman’s criteria (TABLE 1), which is the standard criteria used in The Netherlands, and has the best inter-rater reliability of the current criteria.⁹ Criteria from the International Association of Studies in Pain are the most widely cited in the literature, but are not particularly specific or reproducible.⁹

CHALLENGES TO IMPLEMENTATION

Getting vitamin C started

Recommending 500 mg of vitamin C daily for 7 weeks is a simple and low-cost intervention. Many of our patients will be treated acutely in emergency rooms or by orthopedic surgeons. If these clinicians do not initiate the vitamin C, it may be some time before the primary physician can begin this therapy. We don’t have any information on whether a delay in initiation affects the efficacy of vitamin C.

The evidence presented here is for Colles’s fractures, but CRPS definitely follows other fractures. We are unaware of any physiologic reason why vitamin C therapy would behave any differently for other fracture locations.

It’s a mistake to think CRPS is rare

Perhaps the greatest challenge to implementation is the perception that CRPS is a rare phenomenon or at least generally resolves spontaneously.

The rate in the placebo group (1 in 10 diagnosed at 1 year) and the rates reported through systematic surveillance (1 in 4 diagnosed at some point following Colles’s fracture) struck both us and the clinicians reviewing this study as high.

We suspect symptoms are often

TABLE 2

Rates of complex regional pain syndrome at 1 year: 10% placebo, 2.4% vitamin C

TREATMENT GROUP	PERCENT WITH CRPS	RR (95% CI)	ARR	NNT
Placebo	10%			
Vitamin C				
All doses combined	2.4%	0.24 (0.10–0.60)	0.076	13
200 mg	4%	0.41 (0.13–1.27)	0.06	17
500 mg	2%	0.17 (0.04–0.77)	0.08	13
1500 mg	2%	0.17 (0.04–0.75)	0.08	13

CRPS, complex regional pain syndrome; RR, relative risk; CI, confidence interval; ARR, absolute risk reduction; NNT, number needed to treat.
Source: Zollinger et al, 2007.¹

missed or misdiagnosed. Even with resolution, the symptoms can be bothersome, and quite severe in a few cases (1% to 2%). We think vitamin C 500 mg/day for 7 weeks is well worth recommending. ■

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- Atkins RM. Complex regional pain syndrome. *J Bone Joint Surg Br* 2003; 85:1100–1106.
- Sandroni P, Benrud-Larson LM, McClelland RL, Low PA. Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study. *Pain* 2003; 103:199–207.
- Bickerstaff DR, Kanis JA. Algodystrophy: an under-recognized complication of minor trauma. *Br J Rheumatol* 1994; 33:240–248.
- Field J, Atkins RM. Algodystrophy is an early complication of Colles’ fracture. What are the implications? *J Hand Surg [Br]* 1997; 22:178–182.
- Forouzanfar T, Koke AJ, van Kleef M, Weber WE. Treatment of complex regional pain syndrome type I. *Eur J Pain* 2002; 6:105–122.
- Quisel A, Gill JM, Witherell P. Complex regional pain syndrome: which treatments show promise? *J Fam Pract* 2005; 54:599–603.
- Zollinger PE, Tuinebreijer WE, Kreis RW, Breederveld RS. Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: a randomised trial. *Lancet* 1999; 354:2025–2028.
- Quisel A, Gill JM, Witherell P. Complex regional pain syndrome underdiagnosed. *J Fam Pract* 2005; 54:524–532.

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