Zollinger PE, Tuinebreijer WE, et al. Can Vitamin C Prevent Complex Regional Pain Syndrome in Patients with Wrist Fractures? JBJS Am 2007; 89:1424-31.

Reviewed, no change to conclusions Feb 2017

Design: Randomized clinical trial

Population/sample size/setting:

- 416 patients with 427wrist fractures (75 in men, 352 in women, mean age 62) treated at 3 orthopedics departments in the Netherlands
- Any adult with a wrist fracture was eligible, regardless of treatment choice; non-operative treatment and operative treatment fractures were included in the study
- Although 2137 patients with wrist fractures were eligible for the study, the participation rate was low, due to a possible lack of interest in the emergency department staffs; 961 potential patients were not informed of the study, and 297 potential participants decided not to participate, since they were not willing to be in a placebo group

Main outcome measures:

- Randomized to vitamin C (n=317 patients, 328 fractures) or placebo (n=99patients, 99 fractures)
- Vitamin C doses were randomized at 3 levels: 200 mg (96 fractures), 500 mg (114 fractures), or 1500 mg (118 fractures)
- Vitamin C or identical-appearing placebo was given in a box of 100 capsules, to be taken twice daily for 50 days
- Patients who had been taking vitamin C (only one took 1000 mg/d; the others took no more than 50 mg) were asked to stop during the trial
- Main end point was CRPS within one year of the fracture, defined as at least 4 of these 5: (1) unexplained diffuse pain not normal in relation to the stage of fracture healing, (2) affected hand different in color relative to the other hand and wrist, (3) diffuse edema, (4) difference in skin temperature relative to the other hand and wrist, (5) limited active range of motion of the wrist and fingers not related to the stage of fracture healing
- CRPS assessment was done by a physician not involved in the patient's fracture management and unaware of treatment assignment
- Patients were evaluated at 1 week, at cast removal (4 or 5 weeks), at 6 weeks, 12 weeks, and 26 weeks; after one year, patients were interviewed by telephone or letter
- No one was lost to follow-up
- CRPS was diagnosed more often in the placebo group (10 of 99) than in the vitamin C group (8 of 328)
- In the vitamin C group, the 8 CRPS cases were distributed as follows: in the 200 mg group, 4 of 98; in the 500 mg group, 2 of 114, and in the 1500 mg group, 2 of 118

- All of the CRPS cases were in women, non in men
- The mean age of the CRPS cases was 67.6; the mean age of the non-CRPS was 62.1
- The type of fracture and the type of treatment was not associated with the occurrence of CRPS
- The earliest diagnosis of CRPS was made 30 days after the fracture; the latest was 166 days, and the average was 76 days after the fracture

Authors' conclusions:

- Vitamin C can inhibit the development of CRPS after a wrist fracture
- Because the case definition of CRPS was based on symptoms, the diagnosis of CRPS was not precise, and it cannot be definitively concluded that vitamin C prevents CRPS
- The number of cases of CRPS was low, and the estimates of relative risk are imprecise for this reason
- A recommendation of 500 mg of vitamin C after wrist fractures can be made

Comments:

- Although concealment of allocation is not explicitly described, it is likely that this is satisfactory, since the allocation code was in the possession of the dispensing pharmacist, who would not have contact with the patients
- Patients were asked not to take vitamin C for "the duration of the trial;" it is not clear whether this meant for the 50 days during which the capsules were taken, or for the 12 months of follow-up
- Having no loss to follow-up partly compensates for the low recruitment rate among eligible participants
- The number of cases of CRPS in the different dose levels of CRPS is too few to allow for a dose-response relationship to be determined; although a steady plasma level is reached with 200 mg (authors state), a dose of 500 mg can be defended

Assessment: Adequate for evidence that 500 mg of daily vitamin C can decrease the risk of CRPS after a wrist fracture