Does Vitamin C Reduce Finger Stiffness after Distal Radius Fractures: a Placebo Randomized Controlled Trial.

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PARNTERS HUMAN RESEARCH

DETAILED PROTOCOL

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BACKGROUND & SIGNIFICANCE

The reported prevalence of disproportionate pain and disability among patients recovering from a fracture of the distal radius varies widely, between 1% and 37% in published series,[1-7] perhaps in part because it is poorly defined, known by so many different names, subjective, and unverifiable. In general, physicians ascribe disproportionate pain and disability to a poorly understood pathophysiologic process currently labeled "complex regional pain syndrome", while psychologists understand this as ineffective coping strategies.[8] Studies consistently identify psychological factors (catastrophic thinking in particular) as the most important determinants of pain intensity, finger stiffness, and magnitude of disability after distal radius fractures. [8,9]

Along these lines, it is difficult to interpret the trials suggesting that vitamin C limits the occurrence of complex regional pain syndrome, given that the diagnosis is subjective and variably defined, and the only published trials were performed by advocates of vitamin C.[6,10] We see this reflected in clinical practice, as only 11% of the orthopaedic surgeons always prescribes vitamin C after a distal radius fracture, making it one of the least adhered to recommendations of the AAOS clinical practice guidelines.[11]. In addition, there is a lack of clarity regarding the mechanism by which vitamin C would decrease the incidence of complex regional pain syndrome.[12]

We are interested in the effect of vitamin C after distal radius fractures on objective measurement of finger motion, patient reported outcome measures, and pain intensity, instead of the previously used, subjective and imprecise Veldman criteria for complex regional pain syndrome[13], i.e., (i) unexplained diffuse pain, or (ii) edema, (iii) difference in skin color, or (iv) temperature, or (v) limited active range of motion.

SPECIFIC AIMS

<u>Primary null hypothesis</u>

There is no difference in finger stiffness (distance to palmar crease) between patients taking vitamin C or placebo after six weeks after a distal radius fracture.

<u>Secondary null hypotheses</u>

There is no difference in PROMIS upper extremity function and pain score between patients taking vitamin C or placebo after a distal radius fracture.

There are no factors associated with finger stiffness, PROMIS upper extremity function, and pain intensity after fracture of the distal radius.

SUBJECT SELECTION

Patients will be enrolled in the outpatient clinic at the Hand & Trauma Services at Massachusetts General Hospital.

Inclusion Criteria:

- All adult (age 18 or greater) patients presenting to the Hand and Orthopaedic Trauma Services of the Massachusetts General Hospital (MGH) within two weeks of a fracture of the distal radius, either operatively or nonoperatively treated.

Exclusion criteria:

- Patients with severe kidney failure or kidney stones, known allergy for vitamin C or pregnancy, or patients who are not fluent in either English or Spanish.
- Wrist fracture within the last year on the newly fractured side
- Confounders (baseline characteristics): fracture on the dominant side, current vitamin C supplements.

SUBJECT ENROLLMENT

The treating surgeon at the Hand or Orthopedic Trauma service will determine if the patient is eligible to participate in the study. The surgeon will introduce the study to the patient and answer any questions that the patient may have about the study or about randomization. If the patient agrees to participate, a trained research coordinator (pre-med student) or trained research assistant (PhD or medical student) not involved in clinical care, will obtain consent and begin enrollment procedures. As with the other research studies in this department, there will be no coercion. The research coordinator or research assistant will explain to the patient that participation in this study is completely voluntary and that the patient may withdraw at any time. The research coordinator or research assistant will offer all subjects the opportunity to speak with a licensed physician Investigator during the consent process.

Subjects will be given a copy of the informed consent form, and be informed that their participation is voluntary and that they can withdraw at any time during the study. Subjects make take as long as they like to consider participation, provided they still meet all enrollment criteria.

Study staff will provide the patient with a box of medication, containing either vitamin C or placebo (both completely similar in appearance, taste and smell). The pharmacist involved in preparing the placebo will randomize the boxes of medication according to a list of generated random numbers (Stata 13). The

pharmacist will be the only person with access to the code until conclusion of the trial.

STUDY PROCEDURES

Eligible patient, after informed consent, will be randomly assigned, double-blind, to take either placebo or vitamin C 500 mg for 6 weeks.
At enrollment and 6 weeks (5-8 weeks acceptable) after fracture we will measure: DPC (dig II-V), PROMIS UE CAT, PROMIS pain interference and VAS score; all questionnaires will be filled out in REDCap. If the researcher misses the subject at the 6 week follow-up or if their appointment is outside of the 5-8 week timeframe, three attempts will be made to contact each patient via email and via telephone to complete the 6 week follow-up questionnaires. To address, one of the secondary hypotheses, patients will be contacted 6 months after injury by email; unresponsive patients will be contacted by telephone to assist them with filling out the questionnaires. Three attempts will be made to contact each patient via email and via telephone to complete the follow-up.

Measured variables
At enrollment and 6 weeks (5 to 8 weeks acceptable) after fracture:

- Finger tip distance to palmar crease of fingers II-V (DPC)
- PROMIS Upper Extremity Function (Short form)
- PROMIS Pain Interference Short form
- 0-10 ordinal rating of pain intensity

At 6 months (5 to 8 months acceptable) after fracture:

- PROMIS UE – Short form
- 0-10 ordinal rating of pain intensity

BIOSTATISTICAL ANALYSES

Difference in DPC, function, pain interference and pain will be assessed by Wilcoxon-Mann-Whitney test.

Assuming an effect size of similar magnitude to previous studies[10], power analysis suggests 134 patients provide 80% power to detect a difference with an alpha of 0.05 (effect size 0.50, two tailed Wilcoxon-Mann-Whitney test). As trauma patients are notoriously hard to track, halfway through the study we will assess enrollment and adjust sample size accordingly to account for lost to follow-up.

RISKS AND DISCOMFORTS

Although controversy exists regarding the value of prescribing vitamin C to patients with distal radius fractures, there appears to be limited downside with its use.

Adverse effects of vitamin C are dose-dependent and occur at doses well above the recommended daily dose of 60 mg. Generally, adverse side effects can be avoided with doses below 1000 mg daily in healthy people.[14] In this study, patients who receive the vitamin C treatment will only take 500 mg daily. When several grams of vitamin C are taken at once, diarrhea and abdominal bloating are the most frequent side effects. In addition, renal calculi can precipitate as a result of the ingestion of excess vitamin C. Oxalic acid is produced and renally excreted during vitamin C metabolism. In patients with underlying hyperoxaluria, oxalate excretion is accelerated with vitamin C doses above 1000 mg daily and can contribute to formation of renal calculi. Similarly, hyperuricosuria can occur with large doses of vitamin C, also leading to formation of renal calculi. In patients requiring dialysis, hyperoxalemia can occur with doses as low as 500 mg daily. Therefore, these patients are excluded from our study.

The subject will be inconvenienced by having to complete study related questionnaires and physical examination (about 20 minutes).

POTENTIAL BENEFIT

There may or may not be any direct benefits to the individual subjects. Subjects may benefit from the Vitamin C treatment by experiencing reduced pain and reduced finger stiffness. It is also possible that the subjects will not directly benefit from the treatment, and will recover from their injury as they would under the standard of care treatment outside of this research. Either outcome will contribute to the understanding of the role of vitamin C in the healing of distal radius fractures.

MONITORING AND QUALITY ASSURANCE

Any adverse events will be recorded by a full time research coordinator involved in this project and discussed with the PI immediately. An overview of all adverse events will be discussed at the monthly research meeting at which the PI will decide whether to continue or alter/stop the trial.

The PI will have overall responsibility for the conduct and monitoring of the study and safety of subjects. The research coordinator has an assistive role and will monitor outcomes on a daily basis. The research coordinator will have an assistive role and will be responsible for monitoring outcomes on a daily basis and the research coordinator will discuss all outcomes with the PI on a monthly basis at the research meeting. No independent monitoring will occur. All investigators and study staff will be responsible for reporting adverse effects to the research coordinator. Should any adverse events occur, the research coordinator will report such events to the PI immediately**.** The research coordinator will report adverse events to the IRB in accordance with the IRB adverse event reporting procedures.

There will be a full-time research coordinator responsible for adherence to all IRB rules and guidelines and for the accuracy and completeness of all forms, entries, and

informed consent. The research coordinator is responsible for monitoring all data and adherence to the IRB-approved protocol on a daily basis, and all data and study details will be reviewed with the PI at the monthly research meeting. The research coordinator will report any deviations from the protocol to the PI immediately.

All data from subjects will be filed in locked cabinets in the research office in individualized research folders, independent of clinical charts or any other medical record in electronic format. Any magnetic or electronic information will be saved in password-protected computers to which only research coordinator and persons involved with the research project will have access.

All participants are given a participation number/code at the time of enrollment matching with their received medication box. This code is kept on all data sheets instead of the patient name. Subject information is only accessible by Partners authorized investigators and will not be shared with outside entities. The final results after statistical analysis will not be shared with the any institution.

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