The Effect of Acute High-Dose Vitamin D Supplementation on Fracture Union in Patients With Hypovitaminosis D: A Pilot Study

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Purpose: Vitamin D deficiency has been implicated as a potential etiology of nonunion. Recent studies suggest that hypovitaminosis D occurs in more than two-thirds of orthopaedic trauma patients. Despite its frequency, little information exists on the rate of nonunion after fracture in vitamin D–deficient patients. The purpose of this study is to determine the rate of nonunion in vitamin D–deficient patients with long bone fractures and to evaluate the feasibility of utilizing acute high-dose vitamin D supplementation in patients with hypovitaminosis D.

Methods: 102 adult patients with long bone fractures (humerus, tibia, and femur), presenting to a tertiary Level I trauma center between July 2011 and July 2013, enrolled in an IRB-approved prospective, randomized double-blind placebo-controlled trial to study the effect of acute vitamin D supplementation on fracture union. Serum vitamin D levels were measured for all 102 patients: 89 patients demonstrated vitamin D deficiency (<30 ng/mL) and were randomized to receive either a single dose of 100,000 IU of vitamin D orally within the first 2 weeks following injury (treatment group [TG], N = 44), or a placebo (control group [CG], N = 45). Demographics, fracture location and treatment, vitamin D levels, time to fracture union, and complications including vitamin D toxicity were recorded. Outcomes included healed, nonunion, fixation failure, and lost to follow-up. Nonunion was defined as the absence of bridging bone on 2/4 cortices with a stable implant at 6 months or fixation failure after 6 months. Fixation failure prior to 6 months fell into the fixation failure group. Patients without an outcome and no follow-up for 2 months or more were deemed lost to follow-up. *t*-test and cross tabulations were used to compare groups and verify adequacy of randomization. An intention-to-treat analysis was carried out to build a multivariate model.

Results: Hypovitaminosis D occurred in 87% of enrolled patients (89/102). There were 43 femur fractures (48.3%), 33 tibia fractures (37.1%), and 13 humerus fractures (14.6%). Time to outcomes averaged 5 months for all patients, with a range of 6 weeks to 15 months. TG and CG demonstrated similar demographic and injury characteristics ($P > 0.05$ for all comparisons). Initial vitamin D levels were 16.3 and 16.7 ng/mL in the CG and TG, respectively ($P = 0.831$). 15 randomized patients were lost to follow-up (17%; 8 in the TG, 7 in the CG) and two had failure of fixation prior to union (one per group). No patients exhibited toxicity related to high-dose vitamin D supplementation. The overall nonunion rate for the study cohort was 4.5% (N = 4) with 2.3% in the TG (N = 1) and 6.7% in the CG (N = 3). However, this difference was not statistically significant ($P = 0.855$).

Conclusion: At a Level I trauma center in the Southeastern United States, hypovitaminosis D affected 87% of patients enrolled in this prospective randomized study. Acute high-dose vitamin D supplementation was administered to 44 patients without any adverse effects or toxicity. The nonunion rate observed in the TG was 2.3% versus 6.7% in the CG. To

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discriminate the effect of vitamin D supplementation, using the observed nonunion rates, power analysis requires 830 patients (415 per group), assuming a power of 80%, significance of 5%, and a 20% attrition rate. Further study of the effect of vitamin D on acute fracture healing is warranted.