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Original Article

Efficacy and safety of vitamin D_3 B.O.N intramuscular injection in Korean adults with vitamin D deficiency

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Abstract

Objective: There has been no prospective study that examined intramuscular injection of high-dose vitamin D in Korean adults. The aim of this study was to assess the efficacy and safety of high-dose vitamin D_3 after intramuscular injection in Korean adults with vitamin D deficiency.
Method: This study was a 24-week, prospective, multicenter, randomized, double-blind, placebo-controlled trial. A total of 84 subjects ≥19 and <65 years of age were randomly allocated to either the vitamin D_3 or placebo group in a 2:1 ratio. After randomization, a single injection of plain vitamin D_3 200,000 IU or placebo was intramuscularly administered. If serum 25-hydroxyvitamin D (25[OH]D) concentrations were <30 ng/mL on week 12 or thereafter, a repeat injection was administered.
Results: After a single intramuscular injection of vitamin D_3 to adults with vitamin D deficiency, the proportion of subjects with serum 25(OH)D concentrations ≥30 ng/mL within 12 weeks was 46.4% in the vitamin D_3 group and 3.6% in the placebo group ($p < 0.0001$). The proportion of subjects with serum 25(OH)D concentrations ≥30 ng/mL within 24 weeks was 73.2% in the vitamin D_3 group and 3.6% in the placebo group ($p < 0.0001$). Mean change in serum 25(OH)D concentrations at weeks 12 and 24 after vitamin D_3 injection was 12.8 ± 8.1 and 21.5 ± 8.1 ng/mL, respectively, in the vitamin D_3 group, with no significant changes in the placebo group. Serum parathyroid hormone concentrations showed a significant decrease in the vitamin D_3 group but no change in the placebo group.
Conclusion: Intramuscular injection of vitamin D_3 200,000 IU was superior to placebo in terms of its impact on serum 25(OH)D concentrations, and is considered to be safe and effective in Korean adults with vitamin D deficiency.

Keywords: 25-Hydroxyvitamin D; Koreans; Intramuscular injection; Cholecalciferol

1. Introduction

Vitamin D is essential in bone and mineral metabolism. Accordingly, low vitamin D status is associated with osteoporosis and fractures. Severe deficiency of vitamin D can lead to bone mineralization defects, such as rickets in children and osteomalacia in adults [1,2]. Recently, it has been suggested that vitamin D also has important roles in other tissues besides the skeletal system with its deficiency closely associated with an increased risk of several non-skeletal disorders, such as cancers, infection, autoimmune diseases, cardiovascular diseases, and diabetes mellitus [3–8]. Despite growing awareness of the multiple health benefits of vitamin D, vitamin D deficiency has become a major health concern in modern society. As more people spend a majority of their time indoors, sunlight exposure can be inadequate for cutaneous production of vitamin D. Epidemiological studies have indicated a high

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prevalence of vitamin D deficiency worldwide, especially in Asian countries [9–12]. When serum 25-hydroxyvitamin D (25[OH]D) level of 30 ng/mL was adopted as the cut-off value, the prevalence of vitamin D insufficiency in Korean general population was 86.8% in men and 93.3% in women, which was higher than that of the United States and Canada [13].

The increasing prevalence of limited exposure to sunlight is increasing the importance of dietary sources of vitamin D in maintaining people's vitamin D status in modern society. Fatty fish, egg yolks, and mushrooms are some of the few natural foods that contain vitamin D. In western countries, vitamin D is supplied in the diet of many people by fortifying foods. In the 1930s, a milk fortification program was implemented in the United States to combat rickets [14]. Other vitamin D fortified food products in western countries are breakfast cereals, orange juice, yogurt, and margarine. However, food fortification is uncommon in Asian countries.

A more realistic and easier way to get enough vitamin D is supplementation through either oral or intramuscular route. High-dose vitamin D administered intramuscularly has been effectively used to achieve and maintain individual's sufficient vitamin D status. However, there has been no prospective study of intramuscular injection of high-dose plain vitamin D in Korean adults. This prospective, multicenter, randomized, double-blind, placebo-controlled study was conducted to compare 200,000 IU of vitamin D_3 with placebo in terms of efficacy and safety for 24 weeks after intramuscular injection in Korean adults with vitamin D deficiency.

2. Subjects and methods

2.1. Study subjects

The study subjects were recruited at three different institutions (Yonsei University Severance Hospital, Ajou University Hospital, Dongguk University Ilsan Hospital) in South Korea. After the screening test, male or female subjects with serum 25(OH)D concentration <20 ng/mL who were between 19 and 65 years of age, were enrolled in this study. Reasons for exclusion included history of hypersensitivity reactions to cholecalciferol component; renal disorder (serum creatinine >1.25× upper limit of normal [ULN]); hypercalcemia (serum calcium >10.5 mg/dL); hypercalciuria (urine calcium >4 mg/kg/day or urine calcium [mg/dL]/creatinine [mg/dL] ratio >0.2); suspected calcium stone with clinical findings; sarcoidosis; pseudohypoparathyroidism; malignancies (a patient who was judged to have been cured as 5 years had passed since treatment was able to participate in the study); clinically significant cardiovascular and pulmonary function disorder based on the judgment of the investigator; laboratory test findings as follows: platelet <100,000/mm^3, white blood cell (WBC) < 3000/mm^3, absolute neutrophil count <1500/mm^3, albumin <3.0 g/dL, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >1.5× ULN; treatment with phenytoin or barbiturates within 5 days prior to the investigational product injection; treatment with thiazide diuretics within 3 days prior to the investigational product injection; treatment with glucocorticoids, cholestyramine, colestipol, or cardiac glycosides within 1 day prior to the investigational product injection; requirement of vitamin D supplements during the study; use of tanning booths during the study; pregnant and lactating female; women of childbearing potential who do not use adequate contraception; and individuals deemed inappropriate for study participation by the investigator, currently participating in another clinical trial or having had the last dose of another investigational product within the past 4 weeks. A total of 84 subjects (56 in the vitamin D_3 group and 28 in the placebo group, planned to be assigned in a 2:1 ratio) were enrolled (Fig. 1). Subjects were to be stratified by serum 25(OH)D concentrations (<10 ng/mL or 10–20 ng/mL) in a 1:1 ratio. This study was carried out in accordance with principles of Korea Good Clinical Practice, International Conference on Harmonization-Good Clinical Practice, Declaration of Helsinki, and local laws and applicable regulations. This study was approved by the Institutional Review Board (IRB) at each institution (IRB No. 4-2014-0377, Yonsei University Severance Hospital; IRB NO. AJIRB-MED-CT3-13-397, Ajou University Hospital; IBR No. 2014-16, Dongguk University Ilsan Hospital). All subjects provided their written informed consent for the study after they were provided a detailed description of the experimental procedures and informed that they could withdraw from the study at any time.

2.2. Study design

The 24-week, prospective, multicenter, randomized, double-blind, placebo-controlled clinical trial was conducted between from November 2014 to August 2015 at the three aforementioned institutions in Korea. Following the screening visit, at which inclusion and exclusion criteria were assessed, subjects were randomly assigned to either the vitamin D_3 group or the placebo group in a 2:1 ratio. Vitamin D_3 B.O.N was manufactured by Haupt Pharma Livron (France) as a fragrance free, slightly yellow, transparent injectable solution (200,000 IU [5 mg] as cholecalciferol) contained in a colorless and transparent ampoule. All participants, investigators, pharmacists, and study personnel were blinded to treatment allocation. This study was comprised of period 1 and 2 (Fig. 2). Period 1 was the duration of time from baseline to the end of week 12. During this time, the first injection of vitamin D_3 and tests for primary efficacy assessment were carried out. Period 2 was the duration of time from week 13 to the end of week 24. During this time, subjects who had serum 25(OH)D concentrations <30 ng/mL at the time of week 12 or thereafter received a repeat single injection of the investigational product and subjects ≥30 ng/mL were followed up to week 24 without an additional injection. The enrolled subjects were scheduled to visit 9 times (at week 0, 2, 4, 6, 8, 12, 14, 18, and 24) during the trial and their clinical information and trial data were collected during individual interviews conducted by a well-trained interviewer. All subjects underwent a through medical history review and a physical examination. During the