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## *Proven Safe and Effective in the Treatment of Hypovitaminosis D among otherwise healthy infants and toddlers !*

**Safe** - Conservative regimen of **Bio-D-Mulsion Forte®** supplies necessary vitamin D (as emulsified D3) without the increased risk of hypercalcemia commonly associated with single, large dose therapies – especially important in an outpatient setting.

Additionally, **Bio-D-Mulsion Forte®** contains no artificial colorants or flavorings and no propylene glycol.

**Effective** - One (1) drop daily of **Bio-D-Mulsion Forte®** (2,000 IU) increased 25(OH)D concentrations in vitamin D deficient children 202% in six weeks, effectively tripling 25(OH)D levels.

**Easy to Administer for Greater Compliance** - Simply dispense one (1) drop from the bottle directly onto the tongue each day.

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**Cost Effective** - Of the three regimens tested, the one using **Bio-D-Mulsion Forte®** is by far the most cost effective. (less than a nickel per day - less than $1.50 per month!)


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# *Study Summary* - Vitamin D Treatment in Young Children

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## Treatment of Hypovitaminosis D in Infants and Toddlers

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### Introduction

Vitamin D deficiency, or hypovitaminosis D, appears to be on the rise in young children, with an increased prevalence noted among African American breastfed infants residing in northern latitudes.[1] This deficiency has been identified as the leading cause of rickets among infants, as breast milk contains inadequate amounts of vitamin D to support skeletal health in this age range.[2, 3] Furthermore, numerous sources of evidence now indicate that vitamin D (cholecalciferol) has several important physiologic effects beyond calcium absorption and bone maintenance,[4, 5] and early vitamin D repletion through supervised supplementation may have a positive impact on later neurologic health,[6, 7] immune function,[8, 9] and chronic disease risk.[10, 11] With the reemergence of hypovitaminosis D among infants and toddlers, questions regarding the most appropriate treatment regimen require clarification.

The aim of the present study was to examine prospectively three common treatment short-term regimens for correction of hypovitaminosis D in infants and toddlers. We conducted a randomized clinical trial, treating participants with either daily low dose of vitamin $D_2$, a higher dose of vitamin $D_2$ once weekly, or a low dose of vitamin $D_3$ once daily. This study examined: 1) the efficacy of each treatment in raising serum 25(OH)D and lowering parathyroid hormone (PTH) concentrations; and, 2) the safety and tolerance of each regimen in infants and toddlers, as evaluated through documentation of hypo- or hypercalcemia and reported symptoms.

### Research Design and Methods

#### Subjects

During the cross-sectional screening portion of the study, 380 infants and toddlers, aged 8-24 months, were enrolled consecutively throughout the calendar year from the Children's Hospital Boston Primary Care Center between October 2005 and June 2007. Exclusion criteria for the study included having a chronic disease (e.g. asthma, seizure disorder, sickle cell disease), or the use of oral glucocorticoid over the previous 3 months, or other therapy known to affect vitamin D metabolism. Patients found to be vitamin D deficient (25(OH)D ≤ 20 ng/mL [50 nmol/L]) were invited to participate in the randomized clinical trial which included randomization to one of three vitamin D treatment regimens. The Committee on Clinical Investigation, Children's Hospital Boston, approved the study protocol, and parents or guardians of all participants provided written informed consent.

#### Treatment Protocol

Patients identified to have hypovitaminosis D were randomly assigned to one treatment protocol. The vitamin D treatments included one of three regimens: 2,000 IU oral ergocalciferol (vitamin $D_2$) daily, 50,000 IU vitamin $D_2$ weekly, or 2,000 IU cholecalciferol (vitamin $D_3$) daily. Each group was also prescribed 50 mg/kg/day of elemental calcium to prevent hypocalcemia associated with 'hungry bone' syndrome.[12] Infants received the combined vitamin D and calcium treatment for a course of 6 weeks.

Vitamin D and calcium supplements were each provided in a liquid suspension that was administered orally from a vial directly onto the tongue. The vitamin $D_2$ preparation (200 IU per drop or 0.025 mL) was manufactured by Sanofi-Synthelabo Inc. (Bridgewater, NJ), and doses were provided as 10 drops or 0.25 mL daily for the 2,000 IU dose and 6.25 mL weekly for the 50,000 IU dose; for each vitamin $D_2$ dose. The

vitamin $D_3$ (2,000 IU per drop, oil and water emulsion) was provided by Biotics Research Corporation (Rosenberg, TX) and one drop or 0.025 mL was administered daily from the vial directly onto the child's tongue. Assays of products ensured potency. Two comparisons were formally designated as being of primary interest: daily vitamin $D_2$ vs weekly vitamin $D_2$, and daily vitamin $D_2$ vs daily vitamin $D_3$.

#### Laboratory Measurements

During the baseline and follow-up visits, one blood sample (15 mL) was obtained from each subject. Laboratory samples were processed immediately at both Children's Hospital Boston and ARUP Laboratories (Salt Lake City, UT). Serum 25(OH) D levels were measured at ARUP Laboratories, using a Diasorin chemiluminescent assay (LIAISON®; DiaSorin Inc, Stillwater, MN). This assay accurately quantifies the sum of both 25(OH)$D_3$ and 25(OH)$D_2$. A multi-channel analyzer (Roche Diagnostics, Indianapolis) was used to measure serum calcium, phosphorus, magnesium, and alkaline phosphatase levels on site. Intact PTH was measured by a 2-site chemiluminescence immunoassay (Nichols Institute, San Clemente, CA).

## Results

#### Subjects

Within our clinical sample of 380 infants and toddlers,[13] we identified 40 infants and toddlers to have hypovitaminosis D (25(OH)D ≤ 20 ng/mL [50 nmol/L]). Within this sample of 40 participants, 35 completed the course of therapy (87.5%). All three treatments virtually tripled the 25(OH)D concentration in these vitamin D deficient children. The greatest effect was attained with weekly vitamin $D_2$: from 13.8 to 44.0 ng/mL, an increase of 220%. The next greatest was the effect of $D_3$ (13.7 to 41.2 ng/mL, 202%), followed by daily vitamin $D_2$ (15.7 to 43.9 ng/mL, 182%). Daily vitamin $D_2$ showed an effect 12% lower than weekly vitamin $D_2$ (p=0.66) and 7% lower than daily $D_3$ (p=0.82).

#### Calcium

Baseline calcium concentrations were compared to the current trial participants, each with hypovitaminosis D, to 329 vitamin D replete subjects. The mean change in serum calcium levels was small and similar in the three treatment groups (-3% for vitamin $D_2$ daily, +3% vitamin $D_2$ weekly, +1% vitamin $D_3$ daily).

#### Parathyroid Hormone (PTH)

Eight participants (20%) presented with elevated PTH at baseline (reference range 10-65 pg/mL). All cases returned to normal limits following treatment. There was no significant difference in PTH suppression among the three groups (p=0.74).

#### Alkaline Phosphatase

There was no significant impact of treatment on alkaline phosphatase concentrations.

## Discussion

To our knowledge, this study is the first to compare the efficacy and safety of three common short-term treatment regimens to correct hypovitaminosis D in infants and toddlers. We report no difference in outcome between vitamin $D_2$ daily, vitamin $D_2$ weekly, or vitamin $D_3$ daily for a sample of young children. our study showed that each treatment regimen was equally effective, as well as safe. These data are reassuring to providers, as vitamin $D_2$ daily or weekly, or vitamin $D_3$ daily, combined with elemental calcium, appears to provide an effective and well-tolerated treatment for correcting hypovitaminosis D in infants and toddlers.

Our data provide clinical guidance regarding the appropriate dosage range of vitamin D to treat deficiency in this young population. Among infants, hypercalcemia has been reported with the administration of single high-dose therapy of 300,000 IU[14] or 600,000 IU,[15] as well as daily doses exceeding 10,000 IU daily.[16] While a single 600,000 IU dose has been strongly advocated by one group as a safe regimen and one that eliminates the problem of noncompliance,[18] this recommendation has been met with controversy and, specifically, concerns about hypercalcemia,[14, 17] especially in an outpatient setting. In our study, we report a surprising higher overall incidence of mild hypercalcemia at baseline in contrast to after treatment. All subjects were asymptomatic. There was no statistically significant correlation between the presence of hypercalcemia at baseline and following each tested course of treatment. Therefore, these more conservative regimens of vitamin $D_2$ daily, vitamin $D_2$ weekly, or vitamin $D_3$ daily may rovide the necessary treatment without the increased risk of hypercalcemia commonly associated with single large dose therapies (also known as stosstherapy).[18] The potential toxicity associated with stosstherapy is further

underscored by a recent report that showed hypercalcemia in an infant treated with the equivalent of 4 daily stosstherapy doses.[19]

In summary, we demonstrate that 2,000 IU daily vitamin $D_2$, 50,000 IU vitamin $D_2$ weekly, or 2,000 IU daily vitamin $D_3$ yield equivalent outcomes in the short-term treatment of hypovitaminosis D among otherwise healthy infants and toddlers. These results indicate that pediatric providers can determine the appropriate method of treatment for a given patient or family to ensure compliance, The argument favoring large dose depot therapies for correcting hypovitaminosis D must be reevaluated, as more conservative lower dose therapies may provide a safer method of treatment, especially in the outpatient setting, without the associated risk of hypercalcemia. We recommend early treatment with one of these three treatment regimens, or subtle variations to the dosages studied, to prevent the potential skeletal and extraskeletal problems associated with hypovitaminosis D. Lastly, we do not endorse the use of the current relatively high doses of vitamin D for the long-term prevention of hypovitaminosis D in infants and young children.

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