Prophylactic Effect of Low Dose Vitamin D in Osteopenia of Prematurity: a Clicinical Trial Study

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Abstract- Osteopenia of prematurity (OOP) is a preventable disease. Improved survival of premature newborns is associated with an increased incidence of OOP. The purpose of this study was to compare the prophylactic effects of two low doses of vitamin D (200 and 400 IU/Day) on the clinical, biochemical and radiological indices of the rickets of prematurity. In a randomized clinical trial, 60 preterm newborns with birth weight < 2000 g and gestational age < 37 weeks were randomly divided in two groups. Thirtynewborns received 200 IU/d of vitamin D in group one and 30 ones received 400 IU/day of vitamin D in group two. On the 6th to8th weeks of life, serum calcium, phosphate, alkaline phosphates, and 25 - hydroxy vitamin D concentrationswere measured and x- ray of left wrist and physical examination were performed. Both groups had no difference in biochemical, radiological or clinical presentationof rickets. Currentstudy indicated that low dose vitamin D (200 IU/Day) is enough for prevention of OOP.

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Introduction

Premature newborns are at risk of developing rickets or osteopenia that inverselyis related to the intrauterine gestational age. Clinical rickets usually appears between the 6 to8 weeks of postnatalage. A wrist x-ray at 6th to 8thwks of age remains a practical assessment of the presence of overt rickets. The rates of rickets among premature newborns under 1500gr and 1000gr are 30% and50%, respectively. This rate increases among newborns with weight of800gr to73% (2,4).

The etiology of rickets is multifactorial and includes phosphorous (P), calcium (Ca) and vitamin D deficiency. When premature babies are fed with human milk, and both the Ca and phosphorous P supplies are insufficient. Human milk provides 25% of Ca and P needed for normal bone mineralization. To prevent OOP, vitamin D, Caand P supplementation areneeded. Risk factors for bone disease in preterm infant are include maternal vitamin D deficiency, placental insufficiency and genetic etiology.

Postnatal risk factors include: inadequate supply of Ca and P by prolonged total parenteral nutrition (TPN), vitamin D deficiency, feeding with unsupplemented human milk, and taking medications (diuretics, corticosteroid) and immobility.

Recommendations for vitamin D supply are different in Europe and America. The European Society of Pediatric Gastroenterology and Nutrition (ESPGAN) recommend a dose of 800-1600 IU/d (6). In literature, the recommended dose of vitamin D for prevention of OOP is 400 to 1000 IU/day (2,3,4,7,11-16). The least dose that is reported to prevent OOP is 100IU/Day (6). The American Academy of Pediatrics (AAP) recommends 200 IU/d for infants except neonates (8). Severalstudies indicated that a daily vitamin D dose of 200 IU/d is sufficient to maintain vitamin D status and normal activity. Higher doses of vitamin D may cause hypervitaminosis D that involves risk of hypercalcemia with subsequent complications (2).

The only study about OOP was performed by Alizadeh *et al.,* in Iran (1). In that study 400 IU/d of vitamin D could prevent OOP as well as 1000 IU/Day.

The goal of present study was to compare the prophylactic effects of two low doses of vitamin D (200 -400 IU/Day) on the clinical, biochemical and

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radiological indices of OOP.

Materials and Methods

In this randomized clinical trial authors compared the effects of two low doses of vitamin D on biochemical, radiological and clinical manifestations of OOP. Sixty preterm infants (inpatients or outpatients) referred to Shariati Hospital, Tehran, Iran from May 2010 to May 2012, were enrolled in the study. The inclusion criteria were gestational age of<37 wks and birth weight <2000 g. The exclusion criteria were taking specific medications interacting with vitamin D metabolism (e.g., anticonvulsants, diuretics, corticosteroids and so on) in mother, diabetes mellitus in mother, previous IUGR or SGA baby, chronic use of furosemide in infant and being NPO (non per oral) for more than 2 wks. The withdrawal criteria were failure of taking vitamin D supplements according to the protocol of the study and failure to follow orders such as performing radiography.

Gestational age was determined based on the history of mothers' last menstrual periods, prenatal sonographic findings and postnatal physico-neurological examination. The newborns were randomly divided into two groups by block randomization of two, to receive a 200 IU/d vitamin D (group1) and 400 IU/d vitamin D (group2) since they tolerated full enteral nutrition.

All parents received written instructions about the purpose and protocol of the study after signing an informed consent form which was approved by the local institutional review board for human investigations. All infants in group1 and 29 (96.7%) infants in group 2 could tolerate breast milk and received Casupplement as Cagluconate (90-120 mg/kg/d) and phosphate supplement as phosphate sandose, effervescent tablet (55-75 mg/kg/d). For infants deprived of human milk, premature formula (Prenon), enriched in Caand phosphate was prescribed. In the 6 to 8wks of age, plasma Ca, serum inorganic phosphate and alkaline phosphatase and 25 (OH) vitamin D3were measured; x-ray of left wrist and a through physical examination were carried out.

Ca and P concentration was analyzed using photometry analyser. Serum alkaline phosphatase activity was measured using paranitrophenol reaction method and 25(OH) vitamin D3 by ELISA. Physical examination and x-ray evaluation were made by blinded expert neonatalogists. Diagnosis of OOP was based on: 1-abnormal radiographic findings (osteopenia, bone fractures, intracortical resorption), losing the sharp border (fraying), changing from a convey or flat surface to more concave surface (cupping) of metaphysealedge, widening of the distal end of the metaphysis.

2- Biochemical results including normal or low serum Ca, low serum phosphate, high serum alkaline phosphatase and low Serum 25 (OH) vitamin D3 concentrations.

3-Signs and symptoms of rickets (craniotabes, rickets rosary, wide fontanel, Harrison groove, kyphosis/scoliosis, Potts belly).

Statistical analyses were performed by SPSS version12, software package (SPSS Inc, Chicago, IL), using *Chi*-square and student t-test. *P*-values< 0.05 were considered statistically significant.

Results

In this study, 60 preterm infants in two groups received two prophylactic different doses of vitamin D 200 IU/Day in the first group and 400 IU/Day in the second group. All participated infants had GA of 26 to 36 weeks, and birth weight of 700 gr to 2000 gr.

No difference in two groups in the serum Ca (*P*=0.23), P (*P*= 0.20), Alkaline phosphatase (*P*=0.91) and 25 - Hydroxy vitamin D (*P*=0.86) were seen (Table 1).

No difference in two groups in the decreased calcification of the bone cortex (*P*=0.25), fraying (*P*=1), increased distance metaphyseal of radius and ulnar from wrist bones and density decrease (*P*=0) were found (Table 2).

No difference in two groups in the clinical features including wide fontanele (*P*=0.71), widening of the wrist (*P*=0.55), Harisson groove (*P*=0.31) were seen (Table 3).

Rickets Rosary was not observed in any participantsof the two groups (Table 3).

Table 1. Comparison of radiological results in two groups

	Reduced Bone Content	Fraying	Increased Distance of Metaphyseal	Reduced Bone Density
200 IU/d	(%6.7) 2	(%16.7) 5	(%0) 0	(%0) 0
400 IU/d	(%20) 6	(%16.7) 5	(%0) 0	(%0) 0
P.Value	0.25	1	0	0

Table 2. Comparisen of biochemical results in two groups

	mean±SD Ca	mean±SD Serum P	mean±SD Serum Alkaline Phosphate	mean±SD 25(OH)D Serum
200 IU/d	9.49±0.48	6.12±0.82	796.5±315.45	80.26±24.5
400 IU/d	9.65±0.52	5.78±1.15	788.4±261.7	79.16±26.15
***P*.Value**	0.23	0.20	0.91	0.86

Table 3. Comparison of clinical results in two groups

	Wide fontanels	Widening of the wrist	Harrison groove	Craniotabes
200 IU/d	(%13.3) 4	(%3.3) 1	0	0
400 IU/d	(%16.7) 5	(%6.7) 2	(%3.3) 1	0
***P*.Value**	0.71	0.55	0.31	0

Discussion

Rickets is one of the most important complications of prematurity. Incidence of the OOP is estimated to be 23-32% in very low birth weight infants (< 1500g) and 50% in infants < 1000 g (2). Human milk and formula both supply insufficient Ca and P for normal bone mineralization (6,7,9,14,17-21). Clinical rickets appears between the 6th to 8th postnatal weeks.

DEXA (Dual Energy X-ray Absorptiometry) can measure Bone Mineral Content (BMC) but in routine clinical practice it is performed in few centers and has its own 'baggage,' such as cost, availability and logistic difficulties (4,8). Standard x-ray films are not an accurate assessment for bone demineralization because BMC must be decreased by 20% to 30% or more to be diagnosed by this method (2). However they can detect bone fractures, osteopenia, intracortical resorption, cupping, fraying and increased distance of the distal of the metaphysic (4). A wrist x-ray film at 6 to 8 weeks of age remains a practical assessment of the presence of rickets (2).

Simple biochemical indicators of bone mineralization such as serum alkaline phosphates, and to some extent, serum phosphate, serum Ca and Serum 25 (OH) vitamin D may be an easy way of identifying metabolic bone disease in premature infants(4).

Provision of adequate amounts of Ca, P, and vitamin D significantly decreases the risk of rickets of prematurity (2-4).

Backstrom *et al*., compared the effects of low (200 IU/Day) and high (960 IU/Day) doses of vitamin D on bone mineral accretion, using DEXA, in two small groups of premature infants until three months old. They noticed that there were no differences in bone mineral content and in bone mineral density at three and six months corrected age between the infants receiving low or high dose of vitamin D (15).

AAP has recommended a vitamin D dose of 400IU/day for preterm newborns (14). Koo et al., showed that even as little as 160 IU/Day of vitamin D maintain normal and stable vitamin D status in preterm infants received adequate mineral intake(13).According to Alizadeh P *et al.*, two different doses of vitamin D (400IU/Day and 1000IU/Day) had the same effect in prevention of OOP (1).

Current study indicated that low dose of vitamin D intake; 200 IU/Day has the same protection in bone mineral content as400IU/Day of vitamin D. The authors used biochemical, radiological and clinical criteria to diagnose OOP and there were no significant differences between the control and interventional group for biochemical and radiological features, as well as clinical manifestations.

In the present study, serum 1,25 (OH) D3 concentration in both groups were within the reference limits, indicating sufficient 1-hydroxylation of vitamin D even with a low dose of vitamin D.

The limitation of this study was that authors didn't use DEXA for evaluating BMC.

In conclusion, the authors recommend 200 IU/Day of vitamin D supplement for premature newborn. This low dose of vitamin D, as well as 400IU/Day of vitamin D, can prevent OOP.

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