The efficacy of oral versus parentral vitamin D in treatment of nutritional rickets

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Abstract:

Rickets is the most common form of metabolic bone disease in children. Vitamin D deficiency rickets is clearly a problem in breast-fed infants who do not receive enough vitamin D or adequate sunshine exposure. The study was carried out on 30 patients who had clinical evidence of rickets. Patients were divided into three equal groups. Group A received 600,000U IM once; group B received 20,000U IM three times a week for two weeks and group C received 2000U/day orally for a month. The aim of this study was to compare the effect of different doses of ergocalciferol on serum calcium, phosphorous and alkaline phosphatase. Results show that the serum alkaline phosphatase concentration significantly decreased more in the group B compared to group A and group B (p=0.013 and p=0.001, respectively). Patients who received the intramuscular dose responded promptly, whereas infants who received the oral dosages had less response.

Keywords: 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D, rickets, vitamin D, vitamin D-dependent rickets

(*Rec.Date*: Jul 26, 2012 - *Accept Date*: Aug 17, 2012)

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Introduction

Worldwide, rickets is the most common form of metabolic bone disease in children. Vitamin D deficiency is the main cause of rickets, though nutritional deficiency of calcium and phosphorous generates the same clinical picture [1]. Rickets is clearly a problem in breast-fed infants who do not receive enough vitamin D [1] .Human breast milk does not supply the proper amount of vitamin D [2, 3]. These same infants are also not receiving adequate sunshine exposure for many reasons. Appropriate exposure to sunlight is vital for the production of vitamin D [3, 4].

Previtamin D is obtained from the skin, through initial photoconversion of 7-dehydrocholesterol by ultraviolet light. Direct dietary intake of vitamin D provides an alternative source [5]. In the liver, vitamin D undergoes 25-hydroxylation by 25-hydroxylase, one of several cytochrome P450-containing enzymes (CYPs) involved in vitamin D metabolism[6]. 25-hydroxyvitamin D (25OHD) is the major circulating metabolite of cholecalciferol. It increases in proportion to vitamin D production, and is used as a clinical indicator of vitamin D status [7, 8]. The enzyme 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1/CYP1a), which is found in the kidney, is responsible for 1α-hydroxylation to the active 1,25-dihydroxyvitamin D (1,25(OH)2D. 1,25(OH)2D promotes calcium absorption in the small intestine and regulates calcium levels, permitting normal muscular and neuronal function and ensuring adequate bone mineralization [9].

Hereditary rickets is a form of the disease that is passed down through families. It occurs when the kidneys are unable to hold onto the mineral phosphate [8, 9]. The Symptoms of rickets include: the Bone pain or tenderness ; Arms, Legs, Pelvis & Spine; Dental deformities; Delayed formation of teeth, Decreased muscle tone (loss of muscle strength), Defects in the structure of teeth; holes in the enamel, Increased cavities in the teeth (dental caries) & Progressive weakness; Impaired growth; Increased bone fractures; Muscle cramps; Short stature (adults less than 5 feet tall); Skeletal deformities; Asymmetrical or odd-shaped skull, Bowlegs , Bumps in the ribcage (rachitic rosary), Breastbone pushed forward (pigeon chest), Pelvic deformities & Spine deformities (spine curves abnormally, including scoliosis or kyphosis) [1, 10]. Rickets may be seen in children ages 6 - 24 months. It is uncommon in newborns. The goals of treatment are to relieve symptoms and correct the cause of the condition. The cause must be treated to prevent the disease from returning [11].

Hence, this prospective study aims to determine the efficacy of oral versus parentral vitamin D in treatment of rickets.

Patients and methods

The study was carried out on 30 patients who had clinical evidence of rickets or with deformities characteristic of rickets from hematology clinic at Beni Suef University Hospital.

A local hospital research ethics committee approval was obtained for the patients study. Participation was voluntary, and written informed consent was obtained from the parents or guardians of all the children.

Inclusion criteria:

Children who were 6 months to 2 years of age and who had clinical evidence of rickets or with deformities characteristic of rickets (genu varum, genu valgum and widened wrists,….etc)

Exclusion criteria:

Children were excluded if they were reported to have taken vitamin D or calcium supplements during the 12 weeks before screening or a multivitamin or cod-liver oil (both of which contain some vitamin D) less than 4 weeks before screening. Children were also excluded if they had a history of renal disease, tuberculosis, or liver disease or evidence of any of these disorders on physical examination or laboratory testing. All patients were evaluated by laboratory investigations, detailed history and thorough clinical examination.

Detailed history and thorough clinical examination included name, age, sex, present history with concentration on delayed developmental motor milestone (sitting, standing….), delayed dentation, sun exposure, chest infection, recurrent attacks of diarrhea, increased head circumference, wide anterior fontanelle, broadening of the wrist, kyphosis, presence of rosary beads, harrisson sulcus, longitudinal sulcus or pigeon chest, nutritional history (breast feeding or artificial feeding), onset & type of weaning and family history of similar condition.

Laboratory investigations included measurement of serum calcium, phosphorous and alkaline phosphatase before treatment

This prospective study was done on three parallel groups. Patients were divided into three equal groups A, B and C. Each group consisted of (10) patients. Group (A): Represented patients who received dose of 2000 U (25 ml of pedical syrup which contains 400 IU in each 5 ml) per day orally for one month. Group (B): Represented patients who received dose of 600,000 U (devarol injection) intramuscularly once. Group (C): Represented patients who received dose 20,000 U (Cal D B12 injection) intramuscularly three times a week for two weeks.

The classification of the patients into three groups was done according to the physician prescription. All these patients were subjected to laboratory investigations which included measurement of serum calcium, phosphorous and alkaline phosphatase after treatment to assess the response to treatment.

Statistical analysis

The following tests were used:

The paired-samples t-test was used in repeated measures or correlated group design, in which each subject is tested twice on the same variable. A common experiment of this type involves the before and after design. One-way analysis of variance (ANOVA) test with the application of the Bonferroni correction was used to compare the means of the three groups.

For statistical analysis, Statistical package for social science (SPSS) software version 17 was used (SPSS Inc., Chicago, USA).

Results

The general characters of all patients are present in Table 1. Out of the 30 patients (18 females) who were screened, 20 were not receiving adequate sunshine exposure for many reasons; 25 were breastfed children; 10 had prolong feeding without weaning; 17 had recurrent diarrhea; 5 had convulsions; 28 had delayed motor activity; 26 had delayed teeth eruption; 6 with positive family history; 14 had recurrent chest infection; 14 had bossing of the skull; 11 had open anterior fontanelle; 13 had wide wrists; 10 had bow legs; 4 had kyposis; 12 had rosary beads; 4 had Harrison sulcus; 4 had longitudinal sulcus and 6 had pigeon chest.

Table 1. General characters of all patients

Parameter	Group A No. (%)	Group B No. (%)	Group C No. (%)	Total No. (%)
Sex(male)	5(50)	3(30)	4(40)	12(40.00)
(female)	5(50)	7(70)	6(60)	18(60.00)
Inadequate sun exposure	6(60)	8(80)	6(60)	20(66.70)
Breast feeding	9(90)	7(70)	9(90)	25(83.30)
Artificial feeding	1(10)	3(30)	1(10)	5(16.70)
Prolong feeding without weaning	4(40)	2(20)	4(40)	10(33.30)
Recurrent diarrhea	5(50)	7(70)	5(50)	17(56.70)
Convulsions	1(10)	4(40)	0(0)	5(16.70)
Delayed motor activity	8(80)	10(100)	10(100)	28(93.30)
Delayed teeth eruption	9(90)	8(80)	9(90)	26(86.70)
Family history	1(10)	3(30)	2(20)	6(20.00)
Chest infection	5(50)	7(70)	2(20)	14(46.70)
Bossing of skull	4(40)	5(50)	5(50)	14(46.70)
Open anterior fontanelle	2(20)	6(60)	3(30)	11(36.70)
Wide wrist	5(50)	4(40)	4(40)	13(43.30)
Bow leg	1(10)	5(50)	4(40)	10(33.30)
Kyphosis	0(0)	4(40)	0(0)	4(13.30)
Rosary beads	4(40)	7(70)	1(10)	12(40.00)
Harrison sulcus	0(0)	4(40)	0(0)	4(13.30)
Long sulcus	0(0)	4(40)	0(0)	4(13.30)
Pigeon chest	2(20)	4(40)	0(0)	6(20.00)

Table 2 shows that there was a significant difference between all groups regarding serum phosphorous before and after treatment with p=0.029 &0.014 respectively and also a high significant difference regarding serum alkaline phosphtase with p=0.004.

Table 2. The mean±SD of Laboratory investigations of the three groups

	Group A Mean±SD	**Group B Mean±SD**	**Group C Mean±SD**	**p-value**
Age (Month)	12.8±5.5	14.4±5.8	17.5±5.8	0.192
serum calcium before treatment in mg/dl	9.3±1.5	8.3±2.2	8.1±1.1	0.210
Serum calcium after treatment in mg/dl	10.1±0.9	9.8±1.1	9.3±1	0.249
Serum phosphorus before treatment in mg/dl	4.1±0.9	4.6±0.9	5.4±1.2	0.029*
Serum phosphorus after treatment in mg/dl	4.7±0.6	6.1±1.0	6.1±1.6	0.014*
Serum alkaline phosphtase before treatment in U/L	226.3±113.7	1263.1±1172.6	368.3±119.5	0.004**
Serum alkaline phosphtase after treatment in U/L	214.9±114.6	542.9±508.8	315.4±113.3	0.075

* Significant difference with p<0.05 ** significant difference with p<0.01

The responses to treatment in each group are summarized in Table 3. There was a high significant difference in the decrease in serum alkaline phosphtase between the three groups with p=0.004.

Table 3. The mean±SD of the difference between laboratory measurements of calcium, phosphorous and alkaline phosphtase after and before treatment (the response to treatment)

Parameter	**Group A Mean±SD**	**Group B Mean±SD**	**Group C Mean±SD**	**P-value**
serum Calcium	0.78±0.98	1.23±1.61	1.33±0.90	0.565
serum Phosphorous	0.59±0.57	1.46±1.30	0.80±0.90	0.147
serum Alkaline Phosphtase	-11.36±5.60	-623.36±695.70	-47.11±16.91	0.004**

* Significant difference with p<0.05 ** significant difference with p<0.01

Discussion

30 patients (18 females) completed the study. 20 were not receiving adequate sunshine exposure for many reasons; 25 were breastfed children; 10 had prolong feeding without weaning; 17 had recurrent diarrhea; 5 had convulsions; 28 had delayed motor activity; 26 had delayed teeth eruption; 6 with positive family history; 14 had recurrent chest infection; 14 had bossing of the skull; 11 had open anterior fontanelle; 13 had wide wrists; 10 had bow legs; 4 had kyposis;12 had rosary beads; 4 had Harrison sulcus; 4 had longitudinal sulcus and 6 had pigeon chest.

In this study, there was about 66.7 % of the patients that were not receiving adequate sunshine exposure, 83% were breastfed children, 93.3% had delayed motor activity and 86.7% had delayed teeth eruption. Like most previous studies, the results show that nutritional rickets is more common among breastfed children than in artificial fed children[3, 12-14]. Vitamin D deficiency affects motor activity, teeth formation and causes skeletal deformities. Commonly recommended daily intake of vitamin D is not sufficient if sunlight exposure is limited [15].

Another study found that the most frequent manifestations were enlarged wrist joints, hypotonia, irritability, cranial bossing, wide anterior fontanel, bow legs, delayed teething and walking and Harrison's sulcus with chest rosaries. Short stature was recorded in 30% of patients. Craniotabes and hypocalcemic tetany were the least common presentations and the most frequent biochemical abnormality was high alkaline phosphatase (100%), followed by low phosphate (75%) and low calcium (12.5%) [16]. The mean of serum alkaline phosphatase before treatment in group B was significantly higher than the other groups with p=0.004. This may be due to that this group was the most vitamin D deficient group which required 600,000IU IM vitamin D. Various vitamin D preparations are available in the Egyptian pharmaceutical market, dosages (high versus low), dosing schedules (single versus multiple doses), and administration routes (oral or intramuscular).

In this study, a single intramuscular dose (600,000 IU) of vitamin D in the form of devarol injection were compared to a lower daily oral dosage (2,000 IU daily) for four weeks in the form of 25 ml of pedical syrup daily and another lower multiple intramuscular doses (20,000 IU) five times in two weeks in the form of Cal-D-B12 injection. There was no significant difference between the three groups in the increase in the serum calcium concentration or the serum phosphorous concentration. The serum alkaline phosphatase concentration significantly decreased more in the group B to group A and group B (p=0.013 and p=0.001,

respectively). It was expected that patients who received the intramuscular dose responded promptly, whereas infants who received the oral dosages had no or minimal response [17, 18].

The results show that in group A, there was a significant increase of serum calcium concentration p=0.033, a highly significant increase of serum phosphorous concentration p=0.009 and a highly significant decrease of serum alkaline phosphatase concentration p=0.001. But in group B, there was a significant increase of serum calcium concentration p=0.051, a significant increase of serum phosphorous concentration p=0.010 and a significant decrease of serum alkaline phosphatase concentration p=0.028. While in group C, there was a highly significant increase of serum calcium concentration p=0.002, a significant increase of serum phosphorous concentration p=0.028 and a highly significant decrease of serum alkaline phosphatase concentration p=0.001.

These results indicate that the compliance of the patient is an important issue to get the optimum benefit from treatment of rickets. The patient may respond promptly to oral daily dose if he takes the drug as directed in the prescribed dose regimen.

Another study compared the response to vitamin D alone or in combination with calcium and found that the increase in the serum calcium concentration was greater in the groups that received calcium supplements than in the group that received vitamin D alone. The serum alkaline phosphatase concentration decreased more in the group that received a combination of calcium and vitamin D than in the group that received vitamin D alone ($p<0.001$) or the group that received calcium alone ($p=0.008$); there was no significant different between the calcium group and the vitamin D group ($p=0.06$). However, the final serum alkaline phosphatase concentrations were similar in the calcium group and combination-therapy group [19]. Previous studies have compared three different therapy modes (150,000 IU, 300,000 IU, and 600,000 IU vitamin D p.o.) in infants with nutritional vitamin D deficiency rickets to determine the most effective dosage of vitamin D with least side effects. Serum calcium, phosphorus, alkaline phosphatase, magnesium, serum 25-hydroxycholecalciferol, plasma intact parathormone levels and urinary Ca/creatine ratio were determined; they did not find any difference between the doses in the improvement of rickets. However, hypercalcemia was present in infants who had been administered 300,000 IU and 600,000 IU of vitamin D [20].

On the other hand, a study concluded that Once-yearly intramuscular cholecalciferol injection (600,000 IU) is effective therapy for vitamin D deficiency and confirmed that this therapy

appears to be safe [21]. Soliman AT found that an IM injection of a mega dose of cholecalciferol (10,000 IU/kg) is a safe and effective therapy for treatment of rickets in infants and toddlers with normalization of all the biochemical parameters and healing of radiological manifestations [16]. Hence, vitamin D deficiency rickets is still a health concern, especially among breastfed children. Identification of children at risk early enough to ensure adequate vitamin D and calcium intakes can help prevent the occurrence of bony changes.

Physicians should provide 200 IU of vitamin D per day to all breastfed and non breastfed infants who consume less than 500 mL of vitamin D-fortified formula per day and all children and adolescents who consume less than 500 mL of vitamin D-fortified milk per day, do not get regular sunlight exposure, and do not get 200 IU of vitamin D supplement per day from a multivitamin.

The physician must determine the best treatment strategy for each patient on a case-by-case basis. For example, if compliance is a major concern, the single intramuscular dose may be more appropriate.

Conclusion

Single IM dose of 600,000 IU of vitamin D (ergocalceferol) was more effective in treatment of nutritional rickets than small oral daily dose of 2000 IU dose for a month or small multiple IM dose of 20,000 IU five times in two weeks. However the compliance patient may benefit equally from IM and oral doses.

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