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Comparison of Oral Versus Injectable Vitamin-D for the Treatment of Nutritional Vitamin-D Deficiency Rickets

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ABSTRACT

Objective: To assess the safety and acceptability of a single dose of vitamin-D versus the efficacy of injectable Vitamin-D versus oral vitamin-D.

Study Design: Case control.

Place and Duration of Study: It was carried out at the Department of Paediatrics, Kharadar General Hospital, Karachi, from August 2003 to April 2004.

Methodology: Children of the age of 6 months to 3 years with clinical, biochemical and radiological evidence of vitamin-D deficiency rickets were included. The history, clinical examination, complete blood picture, serum calcium, Phosphorus, alkaline phosphatase and X-ray of wrist joint were done. The children were divided into two groups A and B. Group A was given oral vitamin-D and group B was given intramuscular injection of vitamin-D on the first day and then they were followed for two more visits at 30 and 90 days with clinical, biochemical and radiological examinations to assess the outcome.

Results: There were 50 confirmed cases of rickets in each group. The mean age was 10.9±5.1 months and 14.7±8.1 months in group A and B respectively. In these children, clinical features were weakness, difficulty in walking, frontal bossing, ribcage deformity and widening of wrist were seen. After one dose of vitamin-D (cholecalciferol), there was appreciable gain of weight and height and raised levels of alkaline phosphatase became normal during follow-up. Radiological florid rickets and non-florid rickets in both groups healed clinically during follow-up period. Oral and injectable forms of vitamin-D (cholecalciferol) were effective but injectable form was shown to be statistically significant. There were no undesirable side effects and both forms of treatment were well-tolerated.

Key words: Vitamin-D deficiency rickets. Cholecalciferol. Alkaline phosphatase.

INTRODUCTION

Rickets is a common nutritional health problem in children. Nutritional rickets causes considerable childhood morbidity, disability and remains prevalent in the developing countries of Asia. It is still present in Pakistan's urban economically and rural deprived areas.^{1,2} It is unclear why rickets is so prevalent in tropical countries with abundant sunlight which should prevent vitamin-D deficiency. Its etiology is multifactorial including inadequate dietary intake of vitamin-D, reduced vitamin-D production in dark pigmented skin, inadequate sun exposure because of air pollution, infants remaining indoors, cereal-based diet with high

phytate content, malabsorption, rapid growth of healthy infant, prematurity and low-birth weight, vitamin-D malnutrition in pregnant and lactating mothers and prolonged therapy with anticonvulsant and genetic factors.³⁻¹⁵ Children with nutritional rickets need treatment to prevent them from severe consequences of rickets. The standard treatment¹⁶ for nutritional rickets is vitamin-D. Dietary Cholecalciferol (D3) and supplemental sources are important in prevention and treatment of rickets in children. We conducted a longitudinal case control study to compare the efficacy of injectable vitamin-D (cholecalciferol) with single dose oral vitamin-D, assess the safety and efficacy of it.

METHODOLOGY

This study was conducted at the Paediatric Outpatient Department of Kharadar General Hospital, Karachi, from August 2003 to April 2004. This was a clinical trial in which 100 cases were enrolled. All children from 6 months to 3 years of age with clinical, biochemical and radiological evidence of vitamin-D deficiency rickets were included. Children under 6 months or more than 3 years of age, severely malnourished children with rickets other than nutritional type, or presenting with congenital abnormalities, serious illness during the

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study as follow-up or known hypersensitivity to the product were excluded. After taking informed consent from the parents, history and clinical examination was done and complete blood picture, serum calcium, phosphorus, alkaline phosphatase, and X-ray of wrist joint were done and findings were recorded on performa. Radiological criteria used to define active rickets were osteopenia (bone demineralization), widening of growth plate and metaphyseal cupping.^{17,18} Active rickets was further divided in florid and non-florid type.¹³ Radiological evidence of healing was defined as the presence of new calcification, reduced widening of the growth plate compared with the baseline radiograph.^{17,18} The children were divided into two groups by stratified sampling. Children of group-A were given vitamin-D (cholecalciferol) 200,000 i.u orally on the day of induction (Do) in the study and children assigned to group-B were given vitamin-D (cholecalciferol) 200,000 i.u by intramuscular injection. All children were further followed up for two more visits on thirty (D₃₀) and ninety (D₉₀) days. In the follow-up visits the children were subjected to clinical, biochemical and radiological examination and their findings were recorded. For statistical analysis, ANOVA (repeated measured test) was applied to measure the statistical difference of values in weight, height, hemoglobin and biochemical results of first and follow-up visits. Pearson Chi-square was applied to assess the radiological findings of all patients in both groups. P-value <0.05 was considered as statistically significant.

RESULTS

At the end of the study, the data was analyzed and following observations were recorded. Hundred children were enrolled, 50 in group A (oral) and 50 in group B (injectable) according to the study inclusion criteria. Ninety-six percent of children from group A and 94% from group B completed the full study period. Two patients from group A and 3 patients from group B were lost during follow-up.

Baseline characteristics like age, gender, weight and height are shown in Table I. Weight gain in both groups is statistically significant and same in both groups, while increase in height is statistically significant in group B (injectable group). The symptoms and signs of both groups are shown in Table II. The predominant symptom was weakness (78-84%) and difficulty in walking (74-78%) while signs like frontal bossing, ribcage deformity and widening of wrists were predominant. The hematological and biochemical findings of both groups were compared as shown in Table III. Regarding hematological investigations, the level of hemoglobin improved and biochemically, the level of alkaline phosphatase activity in both the groups became normal

Table I: Baseline characteristics of both groups (oral and injectable vitamin-D).

Characteristics	Group A (oral)	P-value/ratio	Group B (injectable)	P-value/ratio
Age (months)				
Mean±S.D	10.9±5.1		14.7±8.1	
Range	24 (6-30)		28 (6-34)	----
Gender				
Male	36	1:0.39	27	
Female	14		23	1:0.85
Weight (Kg)				
Day 1	7.6±1.5	0.012*	8.1±2.0	
Day 30th	7.9±1.5		8.7±2.0	
Day 90th	8.6±1.4		9.0±2.0	0.027*
Height (cm)				
Day 1	67.0±5.8	0.056**	68.9±7.0	
Day 30th	66.6±10.9		71.6±7.4	
Day 90th	71.0±5.9		73.4±7.1	0.018*

*=Statistically significant at p<0.05; **=Not significant.

Table II: Symptoms and signs of both groups.

Symptoms	Group A (Oral)	Group B (Injectable)
Weakness	42 (84%)	39 (78%)
Frequency of fall	11 (22%)	09 (18%)
Difficulty in walking	37 (74%)	39 (78%)
Leg pain during walking	07 (14%)	07 (14%)
Signs		
Bossing of forehead	32 (64%)	28 (56%)
Wide anterior fontanel	26 (52%)	21 (42%)
Rib cage deformity	29 (58%)	33 (66%)
Harrison sulcus	16 (32%)	11 (22%)
Widening of wrist	37 (74%)	41 (82%)
Genu varum	05 (10%)	07 (14%)
Genu valgum	23 (46%)	27 (54%)
Widening of ankle	11 (22%)	10 (20%)

Table III: Hematological and biochemical findings of both groups (oral and injectable vitamin-D).

	Group A Mean ±SD	P-value	Group B	P-value
A.				
Hematological				
Hemoglobin (gm%)	9.4±1.2		9.3±1.4	
B.				
Biochemical findings				
I. Serum calcium				
Day 1	8.7±0.9		8.2±1.2	
Day 30th	8.9±0.8	0.2277**	8.7±1.0	0.026*
Day 90th	8.8±0.7		8.7±0.9	
II. Serum phosphorus				
Day 1	4.6±1.7		4.7±1.5	
Day 30th	5.5±1.1	0.317**	5.0±1.0	0.898**
Day 90th	5.1±0.9		4.9±1.1	
III. Alkaline phosphatase				
Day 1	580±409		687±498	
Day 30th	385±201	0.013*	469±314	0.009*
Day 90th	295±71		309±149	

*= Statistically significant p<0.05; **= Not significant
 Serum Calcium: 8.1-10.4mg/dl, Phosphorus: 4-7mg/dl,
 Alkaline phosphatase: male (105-289 i.u), Female (97-278 i.u)

during the follow-up period (Table IV). Statistically, the level of calcium was raised in both the groups significantly, while alkaline phosphatase level was reduced in both groups but more (p<0.01) in group B. Radiologically, 58.3% cases in group-A and 59.57% in group-B had shown active florid rickets before

Table IV: Alkaline phosphatase levels and radiological severity of rickets.

	Group A n-48	Group B n-47
*Alkaline phosphatase		
Upto 500 i.u	28	20
500-1000 i.u	11	18
>1000 i.u	9	9
Radiological findings		
**Florid rickets	28	28
**Non-florid rickets	20	19

*Alkaline phosphatase: male (105-289 i.u), Female (97-278 i.u).

**Florid rickets¹³ (osteopenia, widened growth plate, metaphyseal concavity with fraying).

** Non-florid rickets (osteopenia, widened growth plate, irregularity of metaphyseal margin but without concave cupping).

administration of therapy and all of them showed signs of healed rickets during their subsequent visits. Regarding the route of administration of vitamin-D (cholecalciferol), it was seen that the parents preferred the injectable route. There were no undesirable side effects observed in either groups and both oral and injectable forms of the treatment were well-tolerated.

DISCUSSION

In this study, the clinical efficacy of injectable versus oral form of cholecalciferol was compared. There were 50 children in each group. The average age in this study was 10.9±5.1 months in group A and 14.7±8.1 months in group B. In a local study from Lahore, age of rickets children were in the range of 6-11 months.¹⁹ In African country – Ethiopia, rickets children were 6-18 months²⁰ while in Middle East country – Kuwait, the children were under one year.²¹ The male to female ratio was 1:0.4 and 1:0.9 in group A and B respectively. Preponderance of male children in both groups was observed as seen in one of the study from Karachi² with 62% of male, and in Peshawar,⁶ the male children were 62%, while a study from Lahore,¹⁹ recognised male gender as a risk factor. Kharadar General Hospital is located in the old city area of Karachi and comprises of a population of mostly lower and middle classes. The majority of population live in multi-storied congested apartments or small houses with one or two rooms devoid of sunlight and without any courtyards. The women and children wear the local dress (shalwar kameez), which covers most of the skin surfaces except face and hands. The body characteristics like weight and height showed improvement as compared to their first visit prior to oral or injectable dose of vitamin-D (as shown in Table I). In clinical symptoms and signs, the majority of parents/guardians highlighted the symptoms of weakness which is difficult to explain in young infants, possibly it is attributed to hypotonia, which is seen in rickets. Progressive weakness of proximal muscles is a feature of rickets.²² Difficulty in walking, frequent falls, pain in the hands and legs were seen,²³ while in signs widening of wrists, frontal bossing, wide anterior fontanel and rib cage deformity were predominantly seen. An additional

observation was the hemoglobin level improved as compared to the level prior to the administration of vitamin D (cholecalciferol). A high degree of association between iron deficiency anemia and vitamin-D deficiency has been observed.²⁴ Low plasma vitamin D and iron deficiency anaemia often coexist.²⁵ Iron deficiency was found to be a significant risk factor for low vitamin-D. Alkaline phosphatase level remains a reliable and economic biochemical marker for diagnosing vitamin-D deficiency rickets and monitoring the effectiveness of treatment in the clinical setting.²⁶ Radiologically, all cases of rickets (florid or non-florid) showed healed rickets during their subsequent visits. There were no undesirable side effects observed in either group of children and both oral and injectable forms of treatment were well-tolerated. Cost of oral and injectable vitamin-D was almost same. Regarding route of administration of cholecalciferol, the parents preferred intramuscular route.

CONCLUSION

Vitamin-D (cholecalciferol) is effective in the treatment of nutritional vitamin-D rickets in both intramuscular and oral form. The clinical efficacy of vitamin-D (cholecalciferol) by both routes is equally good and there are no side effects in either form. Oral vitamin-D (cholecalciferol; 200,000 i.u) is as effective in the treatment of nutritional vitamin-D deficiency rickets as injectable.

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