STOSS THERAPY AND WEEKLY VITAMIN D THERAPY IN THE MANAGEMENT OF NUTRITIONAL RICKETS IN CHILDREN- A COMPARATIVE STUDY

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ABSTRACT

BACKGROUND

The Aim of the study is to study the risk factors of nutritional rickets in children of age 1-5 years and to compare the effectiveness of classical single mega dose vitamin D administration (stoss therapy) and weekly cholecalciferol administration.

METHODS

50 children of age group 1-5 year with clinical, biochemical and radiological features of nutritional rickets and an equal number of age and gender matched control were included in the study. Their risk factors were compared. Those children with rickets were divided randomly into two groups of equal numbers. For one group, single oral dose of 6,00,000 IU of vitamin D and for the other group, weekly oral dose of 60,000 IU of vitamin D was administered for 8 weeks. All children were given calcium supplementation. Regular follow up was done at 1, 2, 6, 9 and 12 months and the improvement was assessed clinically, radiologically and as per the laboratory results.

RESULTS

Major risk factors for the development of nutritional rickets were prematurity, low birth weight, high birth order, consumption of complementary feeds poor in calcium, lack of adequate sunlight exposure and prolonged exclusive breast feeding. Response to treatment was comparable both clinically and as per the investigation results among those who received single massive dose and those on weekly vitamin D therapy.

CONCLUSION

Increased birth order, prematurity and low birth weight were important risk factors for rickets. Inadequate dietary calcium and inadequate sunlight exposure increased chance of getting rickets. Supplementation of vitamin D and calcium were protective. Inadequate maternal sunlight exposure, lack of antenatal and post-natal calcium and vitamin D supplementation showed a significant association with rickets. The most common clinical feature of rickets was bow legs. Both massive single dose therapy and weekly vitamin D administration were equally effective and revealed no significant difference in clinical, radiological and biochemical response.

KEYWORDS

Nutritional Rickets, Stoss Therapy, Vitamin D, Calcium, Cholecalciferol.

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BACKGROUND

Rickets is a disease of growing bone which occur in children before the fusion of epiphysis and is due to defective mineralization of bone matrix at the growth plate.[1] This disease was an epidemic in the industrialized areas in Europe and North America at the turn of 20th century.[2] By 1960, Rickets was virtually eliminated from most of the developed countries by vitamin D supplementation and cow's milk fortification.[3] But it is still prevalent in developing countries including India and is a re-emerging disease in many other countries.[4] Changing lifestyles with young generation spending more time indoors, consuming modern diets lacking in vitamin D and calcium, and atmospheric pollution contribute to the current epidemic of vitamin D deficiency and rickets.[5] Prolonged exclusive breast feeding (especially if the mother is having vitamin D deficiency) will cause vitamin D deficiency in her baby, leading to rachitic changes.[6]

Stoss therapy is the term used to describe administration of a single massive dose of Vitamin D for the treatment of rickets.[7] It is ideal when compliance is poor, because vitamin D can be stored in adipose tissue for months.[7, 8] But a high dose can lead to hypercalciuria and

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nephrocalcinosis in some children. Hence in many centers, weekly or daily regime are being advocated.[9]

This study aims to determine the risk factors of rickets and to compare the efficacy of two treatment regimens, classical Stoss therapy and weekly vitamin D supplementation.

Aims and Objectives

1. To study the risk factors among children in the age group 1 to 5 years with nutritional rickets.
2. To compare two treatment regimens, Massive single vitamin D administration of 600,000 IU (Stoss therapy) and weekly vitamin D supplementation of 60,000 IU for 8 weeks.

Study Population

Children attending pediatric outpatient department in the age group 1 to 5 years, who are diagnosed (clinically, radiologically as well as based on laboratory results) as having nutritional rickets were included as the cases. An equal number of age and sex matched children without clinical or biochemical evidence of rickets were enrolled as the control group.

Exclusion Criteria

1. Children with rickets having a systemic disease.
2. Children on anti-epileptic drugs.
3. Children having a refractory rickets.
4. Children with conditions mimicking rickets like metaphyseal dysplasia, hypophosphatemia or Blount's disease.

Study Design

This study had two parts-

1. A case control study to determine the risk factors of rickets.
2. A randomized study to compare the response to Stoss therapy and weekly vitamin D therapy.

Study Period- January 2015 – December 2015.

Study Protocol

Children attending pediatric outpatient department having clinical features of rickets were investigated (serum Calcium, phosphorous, alkaline phosphatase, 25 hydroxy vitamin D3, and hand radiology) and were enrolled for the study if clinical, radiological and laboratory results were compatible with the diagnosis of nutritional rickets.

After getting the informed consent, data were collected by interviewing the mother. A detailed dietetic history including the intake of egg, milk, oily fish, green leafy vegetables were noted. A history of calcium supplementation, sunlight exposure and drug intake, skin complexion and significant systemic illness were obtained. Details of sun exposure, including the duration, time and body parts exposed were also evaluated. Antenatal and post-partum calcium supplementation and sunlight exposure were assessed for both cases and controls

Children with rickets were randomly put on oral Stoss therapy (6,00,000 lakh units orally as a single dose) and weekly regime (60,000 units per week for 8 weeks). All these children were supplemented with Calcium (50 mg/kg/day in 2 divided doses) throughout the study period (one year). Both groups were followed up at 1, 2, 6, 9 and 12 months for assessing the response to treatment. X-ray of the hand, serum calcium, phosphorous and alkaline phosphatase were repeated at 1, 6 and 12 months.

Randomization

Simple random.

Statistical Analysis

Done using SPSS software. Pearson Chi square test was done and p value calculated. Independent samples t test was done to compare the mean. A p value less than 0.05 was considered significant.

Observations

A total of 50 cases of nutritional rickets were enrolled for the study after detailed history, physical examination and relevant investigations. An equal number of age and gender matched controls were recruited from the pediatric OPD who had come for minor illness. Mean age group of the study population was 1.57 years. Out of 50 cases, there were 38 (76%) boys. 90% of them were from low socioeconomic class as per the modified Kuppuswami criteria. 11 (22%) were first born. 41 (82%) are having birth weight above 2500 grams. 11 (18%) were preterm. Among control population, all were term babies with birth weight above 2500 grams. 49 cases received breast feeding at least for 6 months. Rest were given formula feeds. Among controls, all were breast fed for at least 6 months. Among cases, 15 (30%) children received complementary feeds rich in calcium (ragi) but majority (70%) received diet deficient in calcium (rice, banana powder or wheat). None of the children in both groups received Vitamin D supplementation during infancy. 37 (74%) of children with rickets were not consuming milk or milk products regularly. 35 (70%) children in the control group were consuming milk and milk products. Oily food is a rich source of vitamin D. Only 14 (28%) cases were regularly consuming oily fish (sardine) whereas in control group, 45 (90%) children were taking oily fish regularly. only 3 (6%) children had adequate sunlight exposure for at least 30 minutes a day. 30 (60%) of controls were exposed to adequate sunlight. Complexion of all children were medium or dark. None of them had fair skin. None of the mothers in both groups had received adequate calcium and vitamin D during pregnancy or during lactation (Table 1).

Characteristics	Cases		Controls		Statistical Significance (p value)
	Frequency	Percentage	Frequency	Percentage	
Term gestation	41	82	50	100	0.002
Primi	11	39	26	52	0.002
Birth weight > 2500 grams	41	82	50	100	0.002
Breast feeding up to 6 month	49	98	50	100	0.315
Complementary feed rich in calcium (ragi)	15	30	38	76	0.000
Milk intake (>200 ml per day)	13	26	30	70	0.000
Oily fish intake	14	28	45	90	0.000
Vitamin D supplementation during infancy	0	0	0	0	0
Sunlight exposure > 30 minutes/day	3	6	30	60	0.000

Table 1. Comparison of Gestation, Feeding and Sun Exposure Among Cases and Controls

Statistical analysis demonstrated a significant association between rickets and higher birth order, low birth weight, prematurity, dietary deficiency of calcium and vitamin D (complementary feeds, dairy products and oily fish) and inadequate sunlight exposure as revealed by significant p-value.

Clinical Features	Frequency	Percentage (%)
Delayed dentition	4	8
Dental caries	5	10
Malnutrition	2	4
Bow legs	37	74
Knock knees	1	2
Frontal bossing	8	16
Rachitic rosary	24	48
Wrist widening	36	72
Harrison sulcus	23	46
Double malleoli	36	72

Table 2. Clinical Features of Children with Rickets

Bowlegs, wrist widening, double malleoli and Harrisons sulcus were the commonest clinical features whereas knock knee and frontal bossing were less common (Table 2) in this study.

The following investigations were carried out in both groups. Serum Calcium, phosphorous, alkaline phosphatase, and hand radiology. Only one child among the cases showed hypocalcaemia. Average serum calcium level of cases was 8.85 mg/dL and those of control group was 9.17 mg/dL. Mean value of serum phosphorous among cases was 4.27 and among control was 4.494. Average value of alkaline phosphatase was 576 IU in cases and 160 IU in controls. Statistical analysis showed significant difference in serum calcium and alkaline phosphatase levels among cases and controls (Table 3).

Laboratory Parameters	Case			Control			P value
	Number	Mean	Standard Deviation	Number	Mean	Standard Deviation	
Serum calcium	50	8.85	0.557	50	9.17	0.259	0.000
Serum phosphorous	50	4.270	0.8044	50	4.494	0.5419	0.106
Alkaline phosphatase	50	576.84	286.895	50	160.38	36.477	0.000

Table 3. Statistical Analysis of Laboratory Parameters

For treatment purpose, cases were divided into 2 groups (group A & B) by simple random method. 25 children received classical Stoss therapy with 6,00,000 IU of Vitamin D as single oral administration (Group A). The other group received 60,000 IU of vitamin D once weekly for 8 weeks (group B). All these children received calcium supplementation at a dose of 50 mg/kg/day in 2 divided doses throughout the study period (one year). All children were followed up at 1, 2, 6, 9 and 12 months for assessing the response to treatment in the form of appearance of healing line in hand x-rays (done at 1, 6 and 12 months) and serum calcium, phosphorous and alkaline phosphatase levels (1, 6 and 12 months).

All the cases showed healing line (provisional zone of calcification) in hand x-rays by the end of one month. There was clinical improvement in the form of decreasing wrist widening assessed by measuring the wrist circumference at the level of ulnar head, decrease in inter trochanteric distance and disappearance of double malleoli. There was also improvement in chest deformities. At the end of treatment, wrist widening and double malleoli were completely disappeared in all cases in both groups. Bowing

of the legs and chest deformity were also improved but some deformity persisted even after following up for one year.

The average serum calcium after one month of treatment was 8.9 mg/dL in both the regime. Average serum alkaline phosphatase values were 340 IU in stoss therapy and 323 IU in weekly regime. At the end of one year both treatment regimen showed similar serum calcium levels (9.2 mg/dL). Alkaline phosphatase levels were 182 IU and 174 IU respectively in stoss therapy and weekly regime. Serum phosphorous values were marginally below in the group B, throughout the study period (Table 4).

Laboratory Investigations	Treatment Regimen	Mean	Standard Deviation	Statistical Significance (p value)
Serum Ca (1 mo)	Stoss therapy	8.948	0.4124	0.190
	Weekly therapy	9.096	0.3747	
Serum P (1 mo)	Stoss therapy	4.53	0.760	0.232
	Weekly therapy	4.30	0.526	
Alkaline Phosphatase (1 mo)	Stoss therapy	340.80	95.748	0.509
	Weekly therapy	323.12	92.264	
Serum Ca (6 mo)	Stoss therapy	9.240	0.2646	0.959
	Weekly therapy	9.244	0.2800	
Serum P (6 mo)	Stoss therapy	4.308	0.4518	0.160
	Weekly therapy	4.484	0.4200	
Alkaline Phosphatase (6 mo)	Stoss therapy	200.64	32.749	0.725
	Weekly therapy	196.64	46.130	
Serum Ca (12 mo)	Stoss therapy	9.200	0.2828	0.716
	Weekly therapy	9.228	0.2574	
Serum P (12 mo)	Stoss therapy	4.154	0.4124	0.502
	Weekly therapy	4.084	0.2882	
Alkaline Phosphatase (12 mo)	Stoss therapy	182.84	19.386	0.123
	Weekly therapy	174.64	17.471	

Table 4. Comparison of Various Laboratory Parameters in Both Treatment Regimen During Follow Up

(Foot note: Serum Ca – Serum Calcium, Serum P – Serum Phosphorous)

From the table 4 it could be inferred that that there was no statistically significant difference in the levels of serum calcium, phosphorous and alkaline phosphatase by the end of one year in both the treatment groups.

Because of financial constraints we couldn't do the estimation of 25- hydoxy vitamin D3 in all children. Hence a statistical correlation was not attempted. The observations are being given in the table 5. There was not much of a difference in the mean value of 25 - hydroxy vitamin D3 after treatment in both groups

Serum 25 –OH Vitamin D3	Group A (Single Dose)		Group B (Weekly Regime)	
	Number	Mean serum 25-OH vitamin D3	Number	Mean serum 25 OH vitamin D3
Before treatment	12	12 ng/ml	8	16 ng/ml
At the end of treatment	9	34 ng/ml	8	31.5 ng/ml

Table 5. Comparison of Serum 25- Hydroxy Vitamin D3 Levels in the Treatment Groups

DISCUSSION

50 cases of nutritional rickets were enrolled for the study and an equal number of age and sex matched controls were also recruited. Most of the children with rickets were between 1-2 years age group and the mean age group of the study population was 1.57 years. In a study by Biloo AG et al,[9] mean age group was 14.1 months. Study by De Lucia et al[10] (mean age 20 months) and Kreiter et al[11] (mean age 15.5 months) also showed the same results.

In a case control study on determinants of rickets by Chali D et al,[12] male gender, twins, high birth order, higher number of siblings were significantly associated with rickets ($p< 0.05$) and exposure to sunlight had a protective effect. In the present study, also rickets was more common among those with high birth order, twins, preterm and children with a high birth order. Higher incidence of rickets in higher birth order could be due to decreased spacing resulting in maternal deficiency of calcium and vitamin D which reflect the nutritional status of the infant.[13]

Breast feeding is essential for the normal growth and development in all infants.[14] But it can't provide enough calcium, vitamin D and other nutrients if not supplemented with good quality complementary feeds at 6 months.[15] Prolonged exclusive breast feeding beyond 6 months had resulted in increased incidence of nutritional rickets according to various studies.[16] In the present study, majority

of children were exclusively breast fed up to 6 months only. In a study by Creig F Munns,[17] the median duration of exclusive breast feeding was 6 months with an inverse association between the length of time of exclusive breast feeding and features of rickets. Kreiter et al demonstrated that breast feeding among African American women had risen dramatically in the past few years.[11]

Universal daily administration of vitamin D (400 IU) to all infants up to one year of age, irrespective of the gestational age or birth weight is the only option to prevent vitamin D deficiency as per many studies.[18, 19, 20] No child in the study group or control group received vitamin D supplementation during infancy. De Lucia et al pointed out that only 15% of their study had received vitamin D supplementation during infancy. This observation may be due to over emphasis given to exclusive breast feeding.[21]

Delayed weaning and weaning to a cereal based diet deficient in calcium had resulted in increased chance of getting rickets. In a study by De Lucia et al,[10] 93% of children were breast fed and 86% of children with rickets were weaned with food poor in calcium. In the present study, 70% of the cases were given complementary feed poor in calcium. According to a study by Fischer PR et al,[22] the main causative factor of rickets in Bangladesh was consuming a complementary feed poor in calcium and vitamin D. a Study by Balasubramanian K[23] had a similar observation. A study by Pettifor MA et al[24] observed that in South Africa, diet in children with rickets were devoid of diary products and high in phytates.

Oily fish such as sardine is a rich source of vitamin D.[25] importance of fish and fish products in the prevention of nutritional rickets was discussed in various studies.[26] In the present study, sardine was a part of diet in only 28% of cases but 90% of controls were consuming sardine regularly. Importance of sun exposure in providing enough vitamin D in children is unquestionable.[27, 28] Unfortunately, even being in a tropical country with adequate sun exposure, rickets is widely prevalent in India.[29, 30] In the present study, inadequate sun exposure was associated with an increased risk for rickets. Several studies reinforce this finding. Studies by Prentice A.[31] VK Ekbote et al,[32] Chali D et al[12] underscored the importance of sun exposure in the prevention of nutritional rickets. Thacher et al[33, 34] observed that darkly pigmented children required three to six times the sunlight exposure compared to light colored children to produce the same amount of vitamin D.

John M Pettifor[24] in his study pointed out that peak age of nutritional rickets was between 10-18 months. Factors that were shown to be important in the pathogenesis of rickets were, prolonged breast feeding, maternal vitamin D deficiency, living in temperate climate, lack of sunlight exposure and darkly pigmented skin. In the middle east and in some African countries, social and religious customs that prevent sunlight exposure were also prevalent.[35]

Clinical features of children with rickets in various studies were almost similar to the present study (table 6)

Clinical Features	De Lucia et al[10]	Alphonsus et al[35]	Present Study
Bowing of legs	76.5	82.2	74
Wrist widening	73.5	66	72
Rachitic rosary	41	53	48
Frontal bossing	23.5	60	16

Table 6. Comparison of Clinical Feature in Children With Rickets (in Percentage)

Mahmoud Rafi et al[35] and Fisher PR et al[36] observed that daily supplementation of vitamin D at a dose of 400 IU in infants increased their vitamin D levels much more than supplementation of lactating mothers with vitamin D at a dose of 2000 IU. Hence it is easier to adopt vitamin D supplementation to all children, rather than supplementing lactating mothers[37, 38, 39]

In the present study, two treatment arms, stoss therapy with single dose of vitamin D3 (60, 0000 IU-group A) and weekly therapy with 60, 000 IU of vitamin D for 10 weeks (group B) were equally effective when followed up for one year. Shah and Finberg[40] after administering 60, 0000 IU of vitamin D and observed that complete resolution of symptoms and radiologic findings were observed in all children with no adverse reactions like hypercalcemia.

A Turkish study by Cesur et al[41] compared the effects of administering 150,000, 300,000 and 600,000 IU of vitamin D and reported that resolution of the disease was similar in all three groups. Six children in the 600,000-dose group developed hypercalcemia, but none of them were symptomatic. Therefore, the authors suggested that administering 150,000 IU of vitamin D might be sufficient to treat rickets, without having the risk of developing hypercalcemia. Oliveri et al had a similar observation.[42]

Gorden et al[43] compared the results of daily and weekly administration of vitamin D and opined that both treatment options showed comparable results. In a study by Emel et al,[44] 21 children each were treated with Stoss therapy and daily (2000 IU daily for 6 weeks) treatment showing comparable results. Akcam et al[45] had observed that the increase in bone mineral densities with two different therapy regimens of vitamin D (single dose of vitamin D of 600,000 IU or 20,000 IU per day for 30 days) in infants with vitamin D deficiency rickets was similar and not superior to each other.

RESULTS

Results of many studies, including the present study underscores the fact that daily and weekly regimes with equal or lower doses of vitamin D are equally effective compared to Stoss therapy with probably lessor risk of hypercalcemia.[46,47] Hence it is argued that daily and weekly therapy are more physiological and effective with less adverse effects compared to single massive dose.[48,49] Stoss therapy is preferred where the compliance is questionable.[50, 51] Effectiveness of various treatment modalities have not received adequate importance in India till recently.[47] Community studies to assess the disease burden, treatment

modalities and preventive measures are yet to be done from India.[46]

CONCLUSIONS

Increased birth order, prematurity and low birth weight were important risk factors for rickets. Inadequate dietary calcium and inadequate sunlight exposure increased chance of getting rickets. Supplementation of vitamin D and calcium were protective. Inadequate maternal sunlight exposure, lack of antenatal and post-natal calcium and vitamin D supplementation showed a significant association with rickets. The most common clinical feature of rickets was bow legs. Both massive single dose therapy and weekly vitamin D administration were equally effective and revealed no significant difference in clinical, radiological and biochemical response.

Limitations of the study and suggestions

Small study population was a major limitation of the present study. Further studies with a large study population are need to consolidate the observation of this study. This is a hospital based study. Hence its observations can't be extrapolated to a larger population. Hence a population based study may be more ideal. Measurement of 25 hydroxy vitamin D3 could be done only in a few cases due to financial constraints and hence the results could not be analyzed.

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Contributions

MV planned the protocol and recruited the patients. MJ assisted VK in the project. VK wrote the manuscript. VK will act as guarantor for this paper.

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