

Effectiveness of STOSS Therapy Verses Alternate Strategy of Vitamin D in the treatment of Nutritional Rickets: A study in Dhaka Shishu Hospital, Dhaka, Bangladesh.

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Abstract

Background: Nutritional rickets remains prevalent in many tropical countries like Bangladesh despite the fact that such countries have ample sunlight. Some postulate that a deficiency of dietary calcium and vitamin D are often responsible for rickets in infancy. It causes considerable disability among children. Nutritional rickets resulting from vitamin D deficiency has become an increasing concern in both developed and developing countries. However, recommended treatment options are either small doses daily supplementation of vitamin D for few months or single-day high-dose vitamin D, an approach referred to as Stoss therapy.²⁷ But it was observed in clinical practice that a significant number of children getting Stoss therapy for nutritional rickets but few of them did not cure from nutritional rickets completely and developed rickets again. Considering the importance of the topics and limited study, this comparative study was designed to assess the effectiveness of Stoss therapy versus Alternate Strategy in nutritional rickets in Bangladeshi children. **Material & Methods:** This was an open label observational comparative study conducted in Dhaka Shishu (children) Hospital for 3-years period. Formal ethical clearance was taken prior commencement of the study. Total 100 children suffering from nutritional rickets were selected according to selection criteria. Written informed consent were taken from the parents of the child. The children were divided into two groups. One administered Stoss Therapy and other administered as Alternate Strategy. Stoss therapy (under proper guide lines of the researcher) was given 50 children under the Stoss therapy group: A, and another 50 children were under Alternate Strategy group: B, and they were given alternate oral dose (2000-5000 IU of vitamin D₂/day for 12 weeks. Before starting therapy clinical features and relevant investigations were recorded and it was compared with the value at 3 weeks, 3 months and 6 months follow up visit both the groups. Recoded data was analyzed by statistical software, SPSS 20 with 95% CI and acceptable 5% error. **Results:** Among the 100 rachitic children mean age was 29.30±2.00 SD months (age range: 12-60 months). Median age was 26 months with 56% male and 44% female respondents. Following Stoss therapy and Alternate Strategy significant clinical improvement was seen at 3 months and almost complete resolution of the most of the features over a period of 6 months in both the groups, Significant improvement of different biochemical parameters (serum calcium, phosphate, ALP, and vitamin 25-OH-D) were seen and restored to almost normal level during 6 months in Stoss therapy. In Stoss therapy at the six month the mean serum vitamin 25-OH-D was 30.22±2.53. On the other hand, in Alternate Strategy at six month the mean serum vitamin 25-OH-D was found 60.12±7.63 which was double of Stoss therapy. Comparatively, better result was found in Alternate Strategy which is statistically significant ($p < 0.001$). Radiological improvement was measured by Thacher's 10 point scale and significant improvement starts at 3 weeks which become completely normal at 6 months post therapy ($p < .001$). **Conclusion:** The Alternate Strategy (that means the oral dose of (2000 - 5000) IU/day vitamin D₂ for 12 weeks) is more superior, effective and safe in nutritional rickets children in Bangladesh than that of single dose/day in Stoss therapy. **Keywords:** Nutritional rickets, STOSS therapy, compliance to Stoss therapy, vitamin D deficiency management, Alternate strategy

I. Introduction

Nutritional rickets remains prevalent in many tropical countries like Bangladesh despite the fact that such countries have ample sunlight. Some postulate that a deficiency of dietary calcium and vitamin D are often responsible for rickets in infancy. Nutritional rickets causes considerable disability among children¹. Though virtually eliminated from Europe and North America by the fortification of foods with vitamin D. Nutritional rickets remains prevalent in many parts of the world, including Africa, the Indian subcontinent, Asia, and in the Middle East²⁻⁴. Rickets has been ranked among the five most prevalent diseases among children in developing countries⁵. So, more emphasis is given in this topic because it is preventable and can be managed by cheaper intervention⁶⁻⁸. The roles of vitamin D deficiency, low dietary calcium intake and the interrelationship between the two in the pathogenesis of NR are discussed. It is now recognized that vitamin D deficiency in the pregnant and lactating mother predisposes to the development of rickets in the breastfed infant.⁸ Beside this, prolonged period of breast-feeding (as breast milk contains negligible amount of vitamin D), cereal based diet, inadequate sun exposure, air pollution, darker skin complexion also predispose NR among the Asian child.⁹ Moreover, several factors were also associated with the disease like increase growth of child, mal-absorption, prematurity, low birth weight and genetic factors of child.⁹⁻¹¹ However, most recent research suggest that low dietary intake of calcium is the prominent risk factor that is closely linked with the disease.¹²⁻¹⁴ Nutritional rickets has been reported in several countries (affluent and low resource countries) during the past three decades.^{5,14} In developing countries, its prevalence ranged from 10-70% particularly where malnutrition is predominate phenomenon.¹⁴⁻¹⁷ In Bangladesh, in some places, it is merely reported sporadically,⁵ while in other areas, up to 9% of the childhood population is clinically affected admitting gender and regional variation.^{14,18,19} However, it is unclear to the researcher why rickets is so prevalent in tropical countries with abundant sunlight which should prevent vitamin-D deficiency.⁹ Clinical studies have demonstrated the efficacy of dietary and supplemental source of vitamin D in resolving nutritional rickets.^{4,9,20,21} Various regimes ranging from daily Vitamin D₂ for several weeks therapy to Vitamin D₃ single day high-dose (Stosstherapy) oral or intramuscular therapy was practiced in several countries including Bangladesh.^{9,22,23} Stosstherapy, a European method in which a dose 300,000- 600,000 IU of vitamin D₃ is administered in divided doses during a 24-hour period followed by supplemental vitamin D₂ (400-600 IU/day) as maintenance therapy has been a well-established practice since the late 1930s.^{24,25} The advantage of intramuscular high-dose therapy over other regimes is avoidance of daily dose, thereby increasing patient compliance and decreasing cost of therapy.^{21,26,27} But it was observed in clinical practice that a significant number of children getting Stoss therapy for nutritional rickets but some of them did not cure from rickets completely and developed rickets again. Considering the importance of the topics and limited study, this comparative study was designed to assess the effectiveness of Stosstherapy verses Alternate Strategy in nutritional rickets in Bangladeshi children.

II. Objectives

Objective: To assess and compare the effectiveness of Alternate Strategy and Stoss therapy in nutritional rickets in Bangladeshi children.

III. Methodology And Materials

This was an observational open label comparative study. This study was carried out in Dhaka Shishu Hospital (DSH), Sher-E-Bangla Nagar, Dhaka, Bangladesh for three years of duration from September 2014 to August 2017. Children aged (1-5) years of age were selected in according to the inclusion and exclusion criteria and followed up total 100 children of nutritional rickets. The children were divided into two groups. One administered Stoss Therapy (300000-600000IU) Vitamin D₃ divided doses in single dose orally and other administered as Alternate Strategy of oral dose (2000-5000IU Vitamin D₂). Both groups, then took Vitamin D₂ orally 600IU with Calcium as maintenance therapy. Written informed consent was taken from the parents and formal ethical approval was taken from the DSH. Patients attending in the DSH for growth failure, muscle weakness or bone changes, such as leg deformities were primarily assessed and evaluated clinically, radiologically and with investigations. For diagnosis several serum biochemical markers including calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), parathormone (PTH), 25-hydroxyvitamin D and others tests were done. For diagnosis of nutritional rickets, cut off value of Vitamin 25-OH-D deficiency was set as <30nmol/l rickets cases with normal PTH like hypophosphatemic rickets, renal rickets-renal tubular acidosis type 1 and 2 and vitamin D-dependent rickets types 1 and 2 were excluded. Besides this, child with history of prematurity,

and disease that may hamper absorption as well as metabolism like intestinal malabsorption, renal or hepatic disease and tumor were also considered as criteria of exclusion. All the subjects were subjected to detail history regarding their feeding practices, concurrent illness and socio-demographic profile. The parents who agreed to expose their child at least 60minutes sun exposure/week and can take maintenance therapy of Vitamin D and Calcium were included into the study. The methodological insight was taken from the study done by Emel T et al.²¹ & Chatterjee D et al.²³. In this study 300, 000- 600,000 IU of vitamin D₃ orally in divided doses every 2 hours over a 12-hr period. At the same time 2000-5000 IU of oral vitamin D₂ for 12 weeks were applied in Alternate Strategy to compare the effectiveness of both the groups. Purposive convenient sampling technique was followed during selection of the study participants and data was collected in three times at 3 weeks, 3 months and 6 months interval. Lower frequency of follow up was planned to increase compliance to therapy in this low resource settings. Data collection was done by the corresponding author and each follow up were recorded in a case record form. Incomplete or missing follow up child was excluded and new child of NR was included in the study. During statistical analysis, repeated measures ANOVA were used to test the difference among biochemical and radiological variable at different follow-ups. Mauchly's test was done to determine the sphericity of data. If the assumption of sphericity found violated Greenhouse-Geisser was used to determine the significance of difference. Post-hoc analysis using Bonferroni adjustment was done to detect significance between follow-up changes. Radiological improvement was measured by Thacher's 10 point scale. Data analysis was done by SPSS 20 version with 95% CI with acceptable 5% error.

IV. Results

A total of 100 children of rickets were included in the study. Mean age was 29.30±2.00 months. Median age was 26 months. Minimum age was 12 months and maximum 60 months. Majority of the children (48%) were aged between 12 to 24 months. 55% patients were male and 44 % were female. See table 1 for details. The children were divided into two groups. Group A administered Stoss therapy and group B administered as Alternate Strategy. Each group belonged to 50 children. Clinical features of rickets of group A: (Stoss Therapy) were noted in all of the subjects at initial visit as well as at subsequent follow-up visits. The most frequent sign was swollen wrist and/or ankle joint (56%), followed in decreasing order by frontal bossing (54%), genu varum (42%), genu valgum (40%), pot belly (20%), Trousseau's sign (18%), rachitic rosary (16%), Harrison's sulcus (6%), open anterior fontanelle (8%) and repeated fracture (2%). In subsequent visits all of the clinical features started to show improvement from 2nd follow up at 3 months and at 6 months frequency of all of them except genu valgum had reduced significantly (for more illustration see table 2). Table 3 shows the biochemical changes during six month follow-up. Mean values of serum calcium, phosphate, alkaline phosphatase (ALP) and vitamin 25-OH-D at initial visit were respectively, 8.11±0.23 mg/dl, 2.66±0.47 mg/dl, 1198.34±242.62 IU/L and 11.18±0.39 ng/ml. Serum calcium, and phosphate was below respective normal range and serum ALP was above the normal range. Mean serum vitamin 25-OH-D at first visit was within deficient range. After initiation of therapy serum calcium, phosphate and vitamin 25-OH-D level increased to normal range within 3 weeks and increased steadily afterwards. Only vitamin 25-OH-D remained relatively constant after 3 months. ALP level decreased to normal level at 3 months and at 6 month the mean serum vitamin 25-OH-D was 30.22±2.73. Improvement in all of the biochemical parameters at all follow-ups were statistically significant (p <0.001). On the other hand, Clinical features of rickets of group B: (Alternate Strategy) were noted in all of the subjects at initial visit as well as at subsequent follow-up visits. The most frequent sign was swollen wrist and/or ankle joint (56%), followed in decreasing order by frontal bossing (54%), genu varum (42%), genu valgum (40%), pot belly (20%), Trousseau's sign (18%), rachitic rosary (16%), Harrison's sulcus (6%), open anterior fontanelle (8%) and repeated fracture (2%). In subsequent visits all of the clinical features started to show improvement from 2nd follow up at 3 months and at 6 months frequency of all of them except genu valgum had reduced significantly (for more illustration see table 2). Table 3 shows the biochemical changes during six month follow-up. Mean values of serum calcium, phosphate, alkaline phosphatase (ALP) and vitamin 25-OH-D at initial visit were respectively, 8.11±0.23 mg/dl, 2.66±0.47 mg/dl, 1198.34±242.62 IU/L and 11.18±0.39 ng/ml. Serum calcium, and phosphate was below respective normal range and serum ALP was above the normal range. Mean serum vitamin 25-OH-D at first visit was within deficient range. After initiation of therapy serum calcium, phosphate, and vitamin D level increased to normal range within 3 weeks and increased steadily afterwards and at six month the mean serum vitamin 25-OH-D was 60.12±7.73. Improvement in all of the biochemical parameters at all follow-ups were statistically significant (p <0.001). Thacher's mean score was 7.0±2.2 at initial visit which improved significantly at consecutive follow-ups (p<0.001). At initial visit, none of the children had normal score. The score started to improve after therapy and 30% had achieved '0' score at 3 weeks, 64% at 3 months and at month 6, all subjects had score 0. In both the groups. However, the association of improving vitamin 25-OH-D between Alternate strategy and Stoss therapy prevailed statistically significant (p <0.001) which signifies Alternate Strategy is more effective than Stoss therapy in improving

vitamin 25-OH- D in nutritional rickets in Bangladeshi children.

Table I: Baseline characteristics of the studied patients. (n=100)

Variable	Frequency	%
Age (months)		
24-Dec	48	48
25-36	26	26
37-48	14	14
49-60	12	12
Mean±SD (months) Median	29.18±14.30	
Range	26	
	Dec-60	
Sex		
Male	28	56
Female	22	44

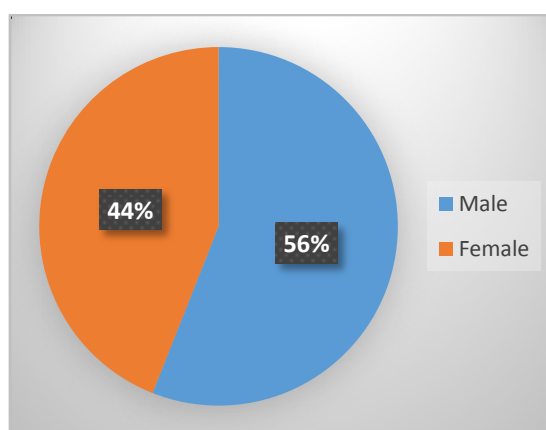


Figure I: Gender distribution of the studied children.(n=100)

Group A: Stoss therapy of vitamin D in nutritional rickets (n=50):

Table II: Comparison of clinical features at day zero (0), 3 weeks, 3 months and 6 months (n=50)

Clinical features, n(%)	0 week	3 week	3 month	6 month
Swollen wrist and/or ankle	28 (56)	28 (56)	16 (32)	8 (16)
Frontal Bossing	27 (54)	27 (54)	20 (40)	13 (26)
Genu Verum	21 (42)	21 (42)	14 (28)	7 (14)
Genu Vulgum	20 (40)	20 (40)	20 (40)	17 (34)
Pot belly	10 (20)	12 (20)	7 (14)	5 (10)
Trousseau's sign	9 (18)	4 (8)	2 (4)	0
Rachitic Rosary	8 (16)	7 (14)	6 (12)	4 (8)
Harrison's sulcus	3 (6)	3 (6)	2 (4)	1 (2)
Open Anterior Fontanelle	4 (8)	4 (8)	1 (2)	1 (2)
Repeat Fracture	1 (2)	-	-	-

Table III: Biochemical changes during follow-up.(n=50)

Biochemical Parameters	0 week	3 week	3 month	6 month	p-value
(Normal Range)	(mean±SD)	(mean±SD)	(mean±SD)	(mean±SD)	
Serum Calcium (8.5-10.5 mg/dl)	8.11±0.23	8.68±0.31	8.86±0.24	9.00±0.27	<0.001
Serum Phosphate (2.8-4.8 mg/dl)	2.66±0.47	3.37±0.52	3.73±0.48	4.38±0.31	<0.001

ALP (<600IU/L)	1198.34±242.62	946.10±191.73	534.58±99.76	321.24±86.11	<0.001
Serum Vitamin 25-OH-D(normal ≥30ng/ml insufficient <30ng/ml deficient 20ng/ml)	11.18±0.39	22.81±6.07	28.61±5.37	30.22±2.53	<0.001

Table IV: Radiological changes during follow-up(n=50)

Thacher's 10 point radiologic score	0 week	3 week	3 month	6 month	P-value
(normal score: 0, abnormal: 1-10)	(mean±SD)	(mean±SD)	(mean±SD)	(mean±SD)	
Mean±SD	7.0±2.2	2.6±2.1	0.62±0.9	0	<0.001
Number of patients with score '0' n (%)	None	15 (30)	32 (64)	0	
*p value determined by repeated measures ANOVA					

Group B: Alternate Strategy of vitamin D in nutritional rickets. (n=50)

Table I: Comparison of clinical features at day zero (0), 3 weeks, 3 months and 6 months (n=50)

Clinical features, n(%)	0 week	3 week	3 month	6 month
Swollen wrist and/or ankle	28 (56)	24 (48)	8 (16)	4 (08)
Frontal Bossing	27 (54)	27 (54)	10 (20)	5 (10)
Genu Verum	21 (42)	21 (42)	12 (24)	6 (12)
Genu Vulgum	20(40)	20(40)	20(40)	17(34)
Pot belly	10 (20)	9 (18)	6 (12)	3 (06)
Trousseau's sign	9 (18)	3 (06)	1 (02)	0
Rachitic Rosary	8 (16)	5 (10)	2 (04)	1 (02)
Harrison's sulcus	3 (06)	3 (06)	2 (4)	1 (2)
Open Anterior Fontanelle	4 (8)	4 (8)	2 (4)	1 (2)
Repeat Fracture	1 (2)	-	-	-

Table II: Biochemical changes during follow-up.(n=50)

Biochemical Parameters	0 week	3 week	3 month	6 month	p- value
(Normal Range)	(mean±SD)	(mean±SD)	(mean±SD)	(mean±SD)	
Serum Calcium (8.5-10.5 mg/dl)	8.11±0.23	8.70±0.31	8.81±0.24	10.10±0.27	<0.001
Serum Phosphate (2.8-4.8 mg/dl)	2.66±0.47	3.38±0.52	3.93±0.48	4.77±0.31	<0.001
ALP (<600IU/L)	1198.34±242.62	947.10±191.73	535.58±99.76	325.25±86.11	<0.001
Serum Vitamin 25-(OH)D (normal ≥30ng/ml insufficient <30ng/ml deficient 20ng/ml)	12.28±0.10	36.18±6.07	47.11±5.37	60.12±7.63	<0.001

Table III: Radiological changes during follow-up (n=50)

Thacher's 10 point radiologic score	0 week	3 week	3 month	6 month	P-value
(normal score: 0, abnormal: 1-10)	(mean±SD)	(mean±SD)	(mean±SD)	(mean±SD)	
Mean±SD	7.0±2.2	2.6±2.1	0.62±0.9	0	<0.001
Number of patients with score '0' n (%)	None	15 (30)	32 (64)	0	
*p value determined by repeated measures ANOVA					

TableIV: Association of improving vitamin D between Alternate Strategy and Stoss therapy at sixmonth. (n=100)

Variable	Alternative Strategy	Stoss Therapy	p-value
Serum Vitamin 25-(OH)D (Mean+SD)	60.12±7.63	30.22±2.53	<0.001
p – Value signifies Alternate Strategy is more effective than Stoss Therapy.			

V. Discussion

The blood level of 25-OH-D defined as vitamin D deficiency remains somewhat controversial. As determined by the measurement of serum concentrations of calcidiol (25- OH-D), vitamin D deficiency is accepted to be present when values are below 15 ng/mL. In children, calcidiol concentrations between 15 and 20 ng/mL indicate vitamin D insufficiency, whereas those 20-30ng/mL are inadequate or insufficient (6, 7). However, these guidelines, based on the recommendations of the Institute of Medicine report, are not accepted by all authorities and remain the subject of ongoing investigations. Alternate guidelines state that a normal 25-OH-D concentration be defined as greater than 30 ng/mL with values of 20 to 30 ng/mL used to define insufficiency and values of less than 20 ng/mL considered as vitamin D deficiency, especially. However, Nutritional rickets is a public-health problem in Bangladesh.¹⁴ Worldwide vitamin D deficiency is the predominant cause of nutritional rickets.²⁸ Several dosing regimens have been developed to replace vitamin D in nutritional rickets.²⁵ Stoss therapy is one of those. Stosstherapy involves use of large dose of vitamin D as a single dose. As vitamin D is stored in the adipose tissue and muscles, after a single large dose continued conversion to active metabolite of vitamin D helps to heal rickets.²³ Hence, it has been a well-established practice to treat nutritional rickets since the late 1930s. Anyway, in this present study, the researcher purposively, 100 children of nutritional rickets were included into two groups. 50 children were given Stosstherapy and 50 children were administered under Alternative strategy and followed up at three weeks, at three months and at six months in order to determine treatment efficacy. Mean age was 29.18±14.30 months. Median age was 26 months. Forty percent (40%) children were aged up to 24 months (2 years). It has been documented that first presentation of nutritional rickets is usually at 6-24 months.¹⁵ Also peak age of vitamin D deficiency rickets happens to be 3-18 months.²⁸ Hence the higher proportion of children of that age group in this study. Slightly higher male prevalence (56%) was noted. A higher male predominance was found in one study investigating role of genetics in rickets.³⁰ but, female predominance was also noted in another comparable study.²³ So, the differences noted in sex could be random. Clinical features of rickets of both the groups were recorded at all visits. The most prevalent clinical sign of Stoss therapy was swollen wrist and/or ankle joint (56%) and at six month it reduced into (16%) Other frequent sign was frontal bossing (54%), at six month it decreased into (26%) and lower limb signs including genu varum (42%) and genu valgum (40%) and at six months they were recorded as (14%) and (34%) Clinical features of rickets shows variable prevalence in difference studies. Ekanem and colleagues found swollen wrist to be the leading sign.³¹ Whereas, knock knee was the most prevalent sign in the study by Karim et al.³² All of the clinical features except genu valgum deformity started to improve at 3 months and reduced significantly at 6 months. Chatterjee and colleagues reported similar findings in their study investigating safety and efficacy of Stosstherapy.²³ Their study involved follow-up of cases for 1 year, they found significant reduction of swollen wrist, frontal bossing, pot belly, rachitic rosary and Harrison's sulcus at 6 months and complete resolution at 12 months. Angular deformity of legs showed less improvement than other signs. Children with mild deformity and earlier age of starting treatment showed the most significant improvement in leg signs. On the other hand, the most prevalent clinical feature of Alternate Strategy at six month were wrist and/or ankle joint was at six month (08%), genu varum (12%) and genu valgum (34%). In Stoss therapy in this study the mean serum calcium, phosphate and ALP started to show statistically significant improvement at 3 weeks (p <0.001) and from 3 months onward these were within normal range and the mean vitamin 25-OH-D level was at deficient range initially and increased to normal range within 3 weeks and at six month it was 30.22±2.53. This finding is supported by studies conducted in India by Chatterjee²³ and in Pakistan by Billo.⁹ But on the contrary in Alternate Strategy the mean serum vitamin 25-OH-D level at six month was 60.12±7.63 which was the double of Stoss therapy and statistically significant (p<0.001). This implies that the Alternate strategy that means the oral dose of (2000- 5000)IU/day vitamin D₂ for 12 weeks therapy is more superior, effective and safe in nutritional rickets children than that of single Vitamin D₃(300,000-600,000IU)divided doses/day in Stoss therapy. The radiological changes prevailed significant in both the cases at six month in this present study.

LIMITATIONS OF THE STUDY

This study was conducted over a limited period of time. Only the entitled patient's got opportunity participated in the study. So, the limited sample size, short duration, and a limited study area were the

limitations of this study. So, with a large sample, vast area and large span of time, the study may be conducted further.

VI. Conclusion And Recommendations

The Alternate Strategy (that means the dose of (2000 - 5000) IU/day vitamin D₂ for 12weeks is more superior, effective and safe in nutritional rickets children in Bangladesh than that of single Vitamin D₃ dose/day in traditional Stosstherapy.

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