

Effectiveness of STOSS Therapy in Nutritional Rickets among Pediatric age Group in Bangladesh

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Abstract: Background: 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. As fewer studies examine the effectiveness of this stoss therapy among Bangladeshi children; the study was designed so.

Materials and Methods: The prospective, cross-sectional study was conducted in Dhaka Shishu (child) Hospital for 3-year period. Formal ethical clearance was taken prior commencement of the study. Total 50 children suffering from nutritional rickets were selected according to selection criteria. Written informed consent were taken from the parents of the child. Stoss therapy were administered under the guidance of the researcher. Before starting therapy base line clinical features and relevant investigation were recorded and it was compared with the value at 3 weeks, 3 months and 6 months follow up visit. Recoded data was analyzed by statistical software, SPSS 23 with 95% CI and acceptable 5% error.

Results: Among the 50 rachitic child, 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, significant clinical improvement was seen at 3 months and almost complete resolution of the most of the features over a period of 6 months. Significant improvement of different biochemical parameters (serum calcium, phosphate, ALP, and vitamin D) were seen and restored to almost normal level during 6 months therapy ($p < .001$). 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: Stoss therapy can be a safe and effective measure for children of Bangladesh with Nutritional rickets.

Keywords: Nutritional rickets, STOSS therapy, compliance to stoss therapy, vitamin D deficiency management

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I. Introduction

Background

Nutritional rickets (NR) is gaining increasing concern all over the world now-a-days.¹ In developing countries, rickets particularly NR, has been ranked among the five most prevalent childhood diseases and cause considerable childhood morbidity, disability.^{2,3} Although the disease remains as an endemic problems in some developing countries, interestingly it has recently re-emerged as a problems in many developed countries as well, where it was thought been almost eradicated.^{1,4-6} More emphasis is given in this topic as because it is preventable and can be managed by cheaper intervention.⁶⁻⁸ 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 contain 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, malabsorption, prematurity, low birth weight, multiple pregnancy, maternal anticonvulsant therapy for long duration, 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 or weekly oral therapy to single 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 of up to 600,000 IU of vitamin D is administered at once or in divided doses during a 24-hour period followed by supplemental vitamin D₂ (400 IU/day) to start after 3 months to prevent or to treat rickets, 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 developed rickets thereafter. Considering the importance of the topics and limited study, the study is designed to assess the effectiveness of stoss therapy for nutritional rickets in Bangladeshi child.

II. Materials and Methods

Design, subjects and Statistics:

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 50 children of nutritional rickets. Written informed consent was taken from the parents and formal ethical approval was taken from the DSH.

Patients attending in the DSH outpatients department for growth failure, muscle weakness or bone changes, such as leg deformities, and suffering from seizures (hypocalcemic tetany) 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 D deficiency was set as <30nmol/l. Rickets cases with normal PTH (hypophosphatemic rickets), phosphaturia (renal rickets-renal tubular acidosis type 1 and 2 and hypophosphatemic rickets), and high levels of calcidiol (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 a criteria of exclusion. Moreover, chronic diseases eg. Tuberculosis, diseases of the skeletal system were also excluded. The child treated with any form of vitamin D deficiency therapy either oral form/injectable form or by partial stoss therapy was a matter of exclusion. All the subject 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 15min sun exposure/week and can afford dietary modification were included into the study. The methodological insight were taken from the study done by Emel T et al.²¹ & Chatterjee D et al.²³ In this study, 600,000 IU of vitamin D₂ orally in 6 doses (100,000 IU/dose) every 2 hours over a 12-hr period, followed by supplemental vitamin D₂ (400 IU/day) to start 3 months after stoss therapy was applied for treatment of the rachitic child.²⁴

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 were 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 was 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. Data analysis was done by SPSS 23 version with 95% CI with acceptable 5% error.

III. Results

Total 50 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. Fifty-six percent patients were male and 44 percent were female. See table 1 for details.

Clinical features of rickets 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 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 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. Only vitamin D level remained relatively constant after 3 months. ALP level decreased to normal level at 3 months and decreased more at 6 months. 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. (See table 4)

IV. Discussion

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.²⁹

In this study 50 children of nutritional rickets were included. They were given Stosstherapy 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 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 were recorded at all visits. The most prevalent clinical sign was swollen wrist and/or ankle joint (56%). Other frequent sign was frontal bossing (54%) and lower limb signs including genu varum (42%) and genu valgum (40%). 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.

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. Mean vitamin D level was at deficient range initially and increased to normal range within 3 weeks. This finding is supported by studies conducted in India by Chatterjee²³ and in Pakistan by Billo.⁹ So, it can be concluded that biochemical correction appears early than the clinical signs and may be evident in as early as 3 weeks. Although other studies reported cases of hypercalcaemia after treatment with single high dose vitamin D therapy³³ no instances

of hypercalcemia or hyperphosphatemia was noted in this study. This implies that single high dose of 600000unit vitamin D is relatively safe in nutritional rickets children above 1 years.

Thacher's10 point radiological score also started to improve from 3 weeks. Cupping, splaying, and fraying which occurred earlier at the distal ulnar region in infants and the knee in older children started to disappear with treatment and all the patients achieved complete radiologic recovery at months six.

V. Conclusion

From the study findings, it can be conclude that in limited resource country like Bangladesh, stoss therapy is safe and effective methods for treatment of nutritional rickets. However, further cohort is recommended to finalize the comments.

Limitation of the study

- Long term and repeated follow up were beyond scope due to lack of fund
- Impact of genetic influence and sun exposure cannot be considered

List of abbreviations:

- ALP- Alkaline phosphatase
- DSH-Dhaka Shishu Hospital
- NNR-Non-nutritional rickets
- NR-Nutritional rickets
- PTH- Parathyroid hormone
- SD-Standard Deviation
- SPSS-Statistical package for social science

VI. Declarations

Ethical consideration

The researcher was duly concerned about the ethical issues related to the study. Formal ethical clearance was taken from the ethical review committee of the Dhaka Shishu Hospital for conducting the study. Formal written consent was taken from the parents of the child. And throughout the study, confidentiality was maintained properly.

Consent of Publication:Not applicable

Availability of data and material: Data and materials supporting our findings in the manuscript will not be shared. It was not in accordance with participants' verbal consent

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Author Contributions:

SPS conceive and developed the concept of the study. Conception and design of this Research were made by MJH, SPS and MAT. MJH & SPS wrote the first draft of the manuscript and MJA, AASMNA, MMA reviewed the draft. All authors read and revised the article and SPS approved the final manuscript.

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VII. List of Tables:

Table 1. Age and sex distribution of subjects (n=50)

Variable	Frequency	Percentage
Age (months)		
12-24	24	48
25-36	13	26
37-48	7	14
49-60	6	12
Mean±SD (months)	29.18±14.30	
Median	26	
Range	12-60	
Sex		
Male	28	56
Female	22	44

Table 2. 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 3. Biochemical changes during follow-up (n=50)

Biochemical Parameters (Normal Range)	0 week (mean±SD)	3 week (mean±SD)	3 month (mean±SD)	6 month (mean±SD)	p *
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 D (normal ≥30ng/ml insufficient <30ng/ml deficient 20ng/ml)	11.18±0.39	35.81±6.07	46.61±5.37	46.22±7.73	<0.001

*p value determined by repeated measures ANOVA

Table 4. Radiological changes during follow-up (n=50)

Thacher's 10 point radiologic score (normal score: 0, abnormal: 1-10)	0 week (mean±SD)	3 week (mean±SD)	3 month (mean±SD)	6 month (mean±SD)	P*
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

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