Original Article

Effect of vitamin D and calcium alone or in combination in the treatment of nutritional rickets

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ABSTRACT

Background: *Nutritional rickets has emerged as a public health problem in Bangladesh during the past two decades, with up to 8% of children being clinically affected in some areas. Insufficiency of vitamin D and dietary calcium is thought to be the underlying cause. Vitamin D administered with or without calcium is commonly regarded as the mainstay of treatment. Calcium alone or in combination with vitamin D has also been used in the treatment of nutritional rickets. So this study was done to assess the effects of vitamin D, calcium or combination of vitamin D and calcium for the treatment of nutritional rickets in Bangladeshi children.*

Methods: *This open labeled randomized comparative study was done in the Department of Paediatrics, Sylhet MAG Osmani Medical College Hospital from July 1, 2010 to June 30, 2012 A total 48 rickets patient was enrolled in this study. After selection of cases patients were divided in to three groups by lottery method. Group A received single i/m dose of vitamin D 4,00,000 IU (2,00,000 IU in each buttock), Group B received calcium (750 mg per day) for 6 weeks and Group C received both calcium (750 mg per day) for 6 weeks and single i/m dose of vitamin D 4,00,000 IU (2,00,000 IU in each buttock). Response was evaluated by serum alkaline phosphatase level and using 10-point radiographic score developed by Thacher and colleagues at baseline, 6 weeks, and 12 weeks.*

Results: *Mean age of the study participants was 35.83 months. Male to female ratio was 2:1. The radiographic score was significantly improved in first and second follow up ($p<0.001$) in all groups. But there was significant difference of improvement in Group C than Group A and Group B. In Group C, the percent reduction from base to first follow up was 80.05±7.04 and 90.65±3 in second follow up which showed quick improvement in combination therapy. Serum alkaline phosphatase also significantly reduced in all three groups.*

Conclusion: *Combination use of vitamin D and calcium in the treatment of nutritional rickets is more effective than prescribing either vitamin D or calcium alone.*

Keywords: *Nutritional rickets, calcium, vitamin D.*

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INTRODUCTION

Rickets, a disease of growing bone, occurs in children only before fusion of the epiphysis and is due to unmineralized matrix at the growth plates.[1] Nutritional rickets remains a global public health concern, particularly in a number of lower–middle income

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countries.[2] Prevalence of nutritional rickets in developed countries also appears to be rising.[3-8]Prevention of nutritional rickets would avoid significant morbidity, so proven effective, preventive and treatment strategies are needed.[8]

Rickets has come into limelight as a public health problem in Bangladesh during the past two decades and was first brought to broad attention in 1991 by Social Assistance and Rehabilitation of the Physically Vulnerable (SARPV) NGO visiting the Chakaria region of South-Eastern Bangladesh after a devastating cyclone. National rickets survey in Bangladesh, 2008 found that the prevalence of rickets in Bangladesh is 0.99%.[9]Helen Keller International conducted surveys in 28 upaziIlas of Bangladesh in 2000 and 2004. Rickets was identified in over half of these upaziIlas, with the highest prevalence in Sylhet and Chittagong divisions.[10]

The peak age of rickets is 3-18 month.[11] Factors that have been shown to be important in the pathogenesis of nutritional rickets at this age include maternal vitaminD deficiency, living in temperate climate, lack of sun exposure and darkly pigmented skin.[12]In the Indian subcontinent, high prevalence of vitamin D deficiency was considered as a major factor for developing rickets in children.[13] Further, low dietary calcium is also considered to play a major role in few countries of Africa.Most of the children in these countries had normal 25-hydroxy vitamin D concentration and high serum 1, 25-dihydroxy vitamin D concentration, indicating adequate intake of vitamin D.[14-16]In one study, it was suggested that low dietary calcium intake was important factor in young children while in adolescent children vitamin D deficiency was mainly responsible for developing rickets.[17]

In our country there is plenty of sunlight throughout the year and therefore the high incidence of rickets is unexpected. The results of study in Chakaria region of Bangladesh demonstrate that active rickets in Chakaria was not usually associated with vitamin D deficiency, and the clinical presentation of rickets in Bangladeshi children was similar to that of African children with calcium-deficiency rickets.[18]

As vitamin D deficiency is considered to be the most common cause of rickets, treatment of rickets is mainly based on administration of vitamin D.[1] Beside the well-known causes of this condition, some investigators have suggested that nutritional rickets seen in sunny areas may be caused by calcium deficiency rather than vitamin D deficiency and that calcium supplementation alone may be effective for treatment.[14,15,19,20]There are two strategies for administration of vitamin D in children with nutritional rickets due to vitamin D deficiency. One is Stoss therapy, 300,000-600,000 IU of vitamin D are administered orally or intramuscularly as a single dose. Alternatively, daily high-dose vitamin D, 2,000-5,000 IU/day over 4-6 week can be given.[1,21]Treatment of calcium deficiency rickets focuses on providing adequate calcium typically as a dietary supplement dose of 350-1000 mg/day of elemental calcium.[1]

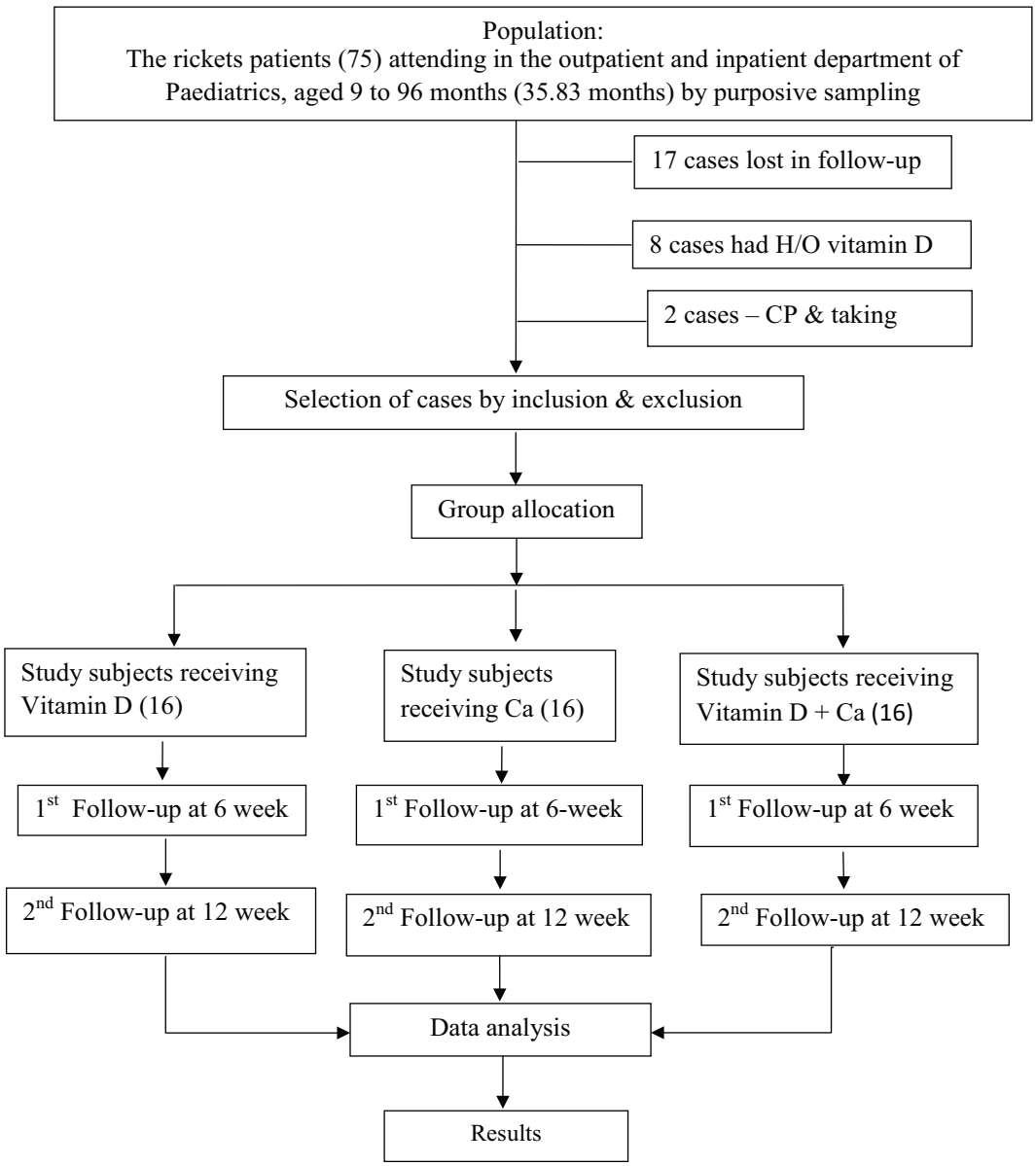
In Bangladesh, the exact etiology of nutritional rickets could not be found due to lack of investigation facilities. So, there is a continuing need to clarify the relative roles of calcium and vitamin D in the etiology and treatment of rickets in different circumstances, which would be helpful for effective integrated treatment of rickets. Thus, this study was designed to determine the most effective treatment regimen for nutritional rickets in Sylhet, Bangladesh.

METHODS

This open labeled randomized comparative study was done in the Department of Paediatrics, Sylhet MAG Osmani Medical College Hospital (SOMCH) from July 1, 2010 to June 30, 2012 to compare the role of combination of vitamin D and calcium with vitamin D or calcium alone in the treatment of nutritional rickets. All the rickets patients attending in the outpatient and inpatient department of Paediatrics who fulfilled the inclusion and exclusion criteria by purposive sampling were enrolled for this study. Children diagnosed as nutritional rickets aged 9months to 96months having any one of the following clinical features like rachitic rosary, Harrisons sulcus, widening of the wrist, knock knee, bowlegs along with following biochemical evidences like serum alkaline phosphatase> 420 U/L (1-9 years), >560 U/L (10-15 years), serum Parathyroid hormone (PTH)>20 ng/dl and children having radiological evidence of nutritional rickets were included in this study. Children who were reported to have taken vitamin D or calcium supplementation before enrolment,taking anticonvulsant therapy (pheno-barbiton, phenytoin), having chronic liver disease, chronic renal disease and familial rickets were excluded. Total 48 cases that were diagnosed as nutritional rickets according to the clinical and lab findings were randomly allocated into three groups. Group allocation of first case was done by lottery method. Then subsequent case was allocated sequentially to subsequent group like ABC, BCA & CAB. First case was selected group B, so subsequent serial was CAB. Thus 16 patients were allocated to each group. Group A received single i/m

dose of 4,00,000 IU vitamin D (Injection Osteo-D of Incepta Pharmaceuticals) 2, 00,000 IU in each buttock. Group B received Tab Calcium carbonate 250 mg (Tab. Calbo Junior of Square Pharmaceuticals) thrice a day for 6 weeks. And Group C received same doses of oral calcium for 6 weeks and a single i/m dose of 4,00,000 IU vitamin D, 2,00,000 IU in each buttock. Parents and guardians were being instructed to continue their usual diet during the study. Radiographs of the wrist and knee were obtained at 6 and 12 weeks after treatment and compared with the baseline radiograph to assess the response of treatment. Serum samples were obtained for alkaline phosphatase at 6 week and 12 weeks to assess the response (Flow chart). Radiographs were assessed by using the method developed by Thacher and colleagues and they were scored according to a 0-10 point scale. The radius and ulna given a score of 2 if the width of the growth plate was increased and accompanied by fraying and cupping. A score of 1 was given if fraying was present but cupping was absent. The femur and tibia each was given a score of 3 if distal femoral epiphysis or the proximal tibial epiphysis appeared widely separated from its metaphysis by a lucent region. A score of 2 was given if the lucency was

Flow chart



only partial and metaphyseal margin was frayed. A score 1 was be given if there was partial lucency with a smooth metaphyseal margin. The maximum score was 10 (2 points for radius, 2 for the ulna, 3 for the femur and 3 for tibia). A score of 1.5 or less after 12 weeks of treatment was considered to indicate nearly complete resolution of the abnormalities.[22] Data were collected by a pre-formed questionnaire. Data were processed and analyzed by using SPSS (statistical package for social science) version-16. Ethical permission was taken from the ethical committee of Sylhet MAG Osmani Medical College. Informed written consent was taken from parents or legal guardians.

RESULTS

Baseline characteristics of the patients in Group A, Group B and Group C were almost similar. There were no significant differences regarding age (Table I). Common clinical manifestations of all the patients of nutritional rickets were widening of wrist, bowing of lower limbs, rachitic rosaryand protruded abdomen (Figure 1). In Group A, radiographic score from baseline to first follow up (2.72±0.58) and second follow up (1.56±0.60) showed highly significant improvement, p=<0.001, serum alkaline phosphatase level m(U/L) also reduced from baseline to first follow up (581.25±119.77) and second follow up (393.13±87.00) and it is highly significant improvement p=<0.001. Treatment with Calcium alone (group B) also showed similar improvement like treatment with vitamin D alone (group A). In first follow up radiographic score reduced to 2.63±0.50 and 1.53±0.62 in second follow up. Improvement of alkaline phosphatase level was also significant. In combination group (group C) improvement is much rapid than other group. In first follow up radiographic score was (1.31 ± 0.25) and in second follow up (0.63 ± 0.22) and it is also highly significant p=<0.001 improvement (Table II). The radiographic improvement between group A and group B is almost similar, there was no significant difference (Table III). There was significant difference in radiographic score between group A and group C, p= >0.001 (Table IV). In comparing among group B and group C, improvement in group C is highly significant, p=<0.001 (Table V).Serum alkaline phosphatase level was reduced in both A and B groups in first follow up and second follow up. But in between group A and group B, improvement in group A is significant (Table VI). In comparison between group A and group C, Serum alkaline phosphatase level was significantly reduced in first follow up and second follow up in group C (Table VII). In comparison between group B and group C serum alkaline phosphatase level was significantly reduced in group C in second follow up but in first follow up the reduction was not significant, p=>0.05 (Table VIII).

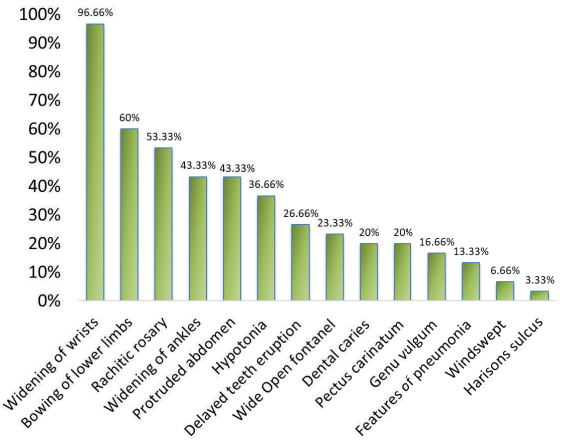


Figure 1 *Distribution of study population by clinical findings of cases (N=48)*

Table I Baseline characteristics of the study population (N=48)

Baseline characteristics	Group			P Value
	Group A	Group B	Group C	
Age (months)	29.75 ± 10.09	39.25 ± 21.60	33.75 ± 16.95	*>0.05 ns
BMI (kg/m^2)	14.93 ± 1.00	14.17 ± 1.09	14.31 ± 0.75	*>0.05 ns
Male	12 (75.0%)	9 (56.3%)	10 (62.5%)	**>0.05ns
Female	4 (25.0%)	7 (43.8%)	6 (37.5%)	
PTH (ng/dl)	46.51 ± 10.50	43.31 ± 11.87	44.81 ± 9.48	*>0.05ns
X-Ray Score	7.94 ± 1.88	7.13 ± 1.74	7.06 ± 1.84	*>0.05 ns
Alkaline Phosphatase (U/L)	818.63± 170.40	785.38± 131.15	800.00± 153.32	*>0.05 ns

*P-value reached from unpaired t-test **P-value reached from chi square test P=>0.05 = not significant(ns)

Table II Efficacy of Vitamin D (Group A), Calcium (Group B) and combined Vitamin D and Calcium (Group C) in the treatment of nutritional rickets

		Baseline	Follow up 1	Follow up 2	P value*
Group A(n=16)	Xray score	7.94 ± 1.88	2.72 ± 0.58	1.56 ± 0.60	<0.001^{hs}
	Alkaline Phoshphatase (U/L)	818.63± 170.40	581.25± 119.77	393.13±87.00	<0.001^{hs}
Group B(n=16)	Xray score	7.13 ± 1.74	2.63 ± 0.50	1.53 ± 0.62	<0.001^{hs}
	Alkaline Phoshphatase (U/L)	785.38± 131.15	494.38± 99.46	338.13± 39.53	<0.001^{hs}
Group C(n=16)	Xray score	7.06 ± 1.84	1.31 ± 0.25	0.63 ± 0.22	<0.001^{hs}
	Alkaline Phoshphatase (U/L)	800.00± 153.32	444.38± 73.03	286.88± 60.85	<0.001^{hs}

* P-value reachedfrom unpaired t-test P=<0.001= highly significant (hs)

Table III X-ray score in group A and group B

X-ray score(Mean ± SD)	Group		P value*
	Group A (n=16)	Group B (n=16)	
Base Line	7.94 ± 1.88	7.13 ± 1.74	>0.05^{ns}
Follow Up 1	2.72 ± 0.58	2.63 ± 0.50	>0.05^{ns}
Follow Up 2	1.56 ± 0.60	1.53 ± 0.62	>0.05^{ns}

* P-value reached from unpaired t-test P=>0.05 = not significant (ns)

Table IV X-ray score in group A and group C

X-ray score (Mean ± SD)	Group		P value*
	Group A (n=16)	Group C (n=16)	
Base Line	7.94 ± 1.88	7.06 ± 1.84	>0.05^{ns}
Follow Up 1	2.72 ± 0.58	1.31 ± 0.25	<0.001^{hs}
Follow Up 2	1.56 ± 0.60	0.63 ± 0.22	<0.001^{hs}

* P-value reached from unpaired t-test P= >0.05 = not significant (ns) P= <0.001= highly significant (hs)

Table V X-ray score in group B and group C

X-ray score (Mean ± SD)	Group		P value*
	Group B (n=16)	Group C (n=16)	
Base Line	7.13 ± 1.74	7.06 ± 1.84	>0.05^{ns}
Follow Up 1	2.63 ± 0.50	1.31 ± 0.25	<0.001^{hs}
Follow Up 2	1.53 ± 0.62	0.63 ± 0.22	<0.001^{hs}

* P-value reached from unpaired t-test P= >0.05 = not significant (ns) P= <0.001= highly significant (hs)

Table VI Serum alkaline phosphatase in group A and group B

Serum alkaline phosphatase (U/L) (Mean ± SD)	Group		P value*
	Group A (n=16)	Group B (n=16)	
Base Line	818.63 ± 170.40	785.38 ± 131.15	>0.05^{ns}
Follow Up 1	581.25 ± 119.77	494.38 ± 99.46	<0.05^{s}
Follow Up 2	393.13 ± 87.00	338.13 ± 39.53	<0.05^{s}

* P-value reached from unpaired t-test P= >0.05 = not significant (ns) P= <0.05 = significant (s)

Table VII Serum alkaline phosphatase in group A and group C

Serum alkaline phosphatase	Group		P value*
(Mean ± SD)	Group A (n=16)	Group C (n=16)	
Base Line	818.63 ± 170.40	800.00 ± 153.32	>0.05^{ns}
Follow Up 1	581.25 ± 119.77	444.38 ± 73.03	<0.001^{hs}
Follow Up 2	393.13 ± 87.00	286.88 ± 60.85	<0.001^{hs}

* P-value reached from unpaired t-test P= >0.05 = not significant (ns) P= <0.001= highly significant (hs)

Table VIII Serum alkaline phosphatase in group B and group C

Serum alkaline phosphatase (U/L)	Group		P value*
(Mean ± SD)	Group B (n=16)	Group C (n=16)	
Base Line	785.38 ± 131.15	800.00 ± 153.32	>0.05^{ns}
Follow Up 1	494.38 ± 99.46	444.38 ± 73.03	>0.05^{ns}
Follow Up 2	338.13 ± 39.53	286.88 ± 60.85	<0.01^{hs}

* P-value reached from unpaired t-test P= >0.05 = not significant (ns) P= <0.01= highly significant (hs)

DISCUSSION

Nutritional rickets remains prevalent among children in our country mainly Sylhet and Chittagong region.[10] In children it is usually considered primarily due to deficiency of vitamin D but several studies in tropical and subtropical countries (Nigeria andSouth Africa) have suggested that in these countries, a low dietary intake of Calcium has an important role.[14,15] These studies reported that children with rickets had a response to Calcium therapy, but there are very few studies that compared the effective response to a combination of Calcium and vitamin D.

Mean age of the children in this study was 35.83 months with the age range of 9 months to 96 months. Shohela et al[23] in their study found the mean age of rickets as 49.36 months with age range 9 months to 156 months. This mean age was more or less consistent with this study.

Patient with clinical rickets confirmed by radiological and biochemical features and who were not on any treatment prior to presentation were provisionally included in this study. Among all children, 66.6% were male which was also consistent with the studies of Shohela et al[23] and Siddiqui et al[24]. Because boys tend to have greater linear bone growth than girls, rickets occur more frequently in boys than in girls.[25]

In this research, it was found that most of the children with rickets were underweight and having lower BMI. This finding was similar to a study conducted in Saudi arabia[26] which found rachitic children to have a lower BMI than nonrachitic children.

The current study found that common clinical manifestations of nutritional rickets were widening of wrist (96.7%), bowing of lower limbs (60%), rachitic rosary (53%), protruded abdomen (43.3%) and Shohela et al[23] found that 90% of child had widening of wrist, 80% had rachitic rosary, 45% had genu valgum, these findings support the result of current study. Majeed et al[27] and Siddiqui et al[24] described the nearly similar clinical findings in their studies in Pakistan.

Radiological score of 1.31±0.25 at 6 weeks of treatment and 0.63±0.22 after 12 weeks of treatment in combination therapy of group C in current study indicates complete resolution and this was significant improvement when comparing with group A and group B. Similar result was found by Kutluk et al,[28]Thacher et al[29]and Aggarwal et al.[30]

This research showed significant improvement of treatment with vitamin D, Calcium or in combination of both. But improvement of clinical, radiological and biochemical finding in Calcium group and vitamin D group was slower than those in combination group.

However, Thacher et al.[31] found better responses with Calcium alone and in combination of vitamin D with Calcium than with vitamin D alone in Nigerian children.Because nutritional rickets in most Nigerian children results from inadequate dietary calcium intake, rather than vitamin D deficiency.

When comparing the improvement between groups there was significant difference in improvement in group C in comparison with group A and group B.At six weeks and twelve weeks follow up serum alkaline phosphatase level also decreases more in the group that received a combination of Calcium and vitamin D than in group that received Calcium or vitamin D alone. This improvement was also significant between Calcium group and vitamin D group. But it was highly significant when comparing between group A and group C which had similarity found by Aggarwal et al.[30].

Oginni and colleagues[20]and Thacher et al[32] found healing with Calcium after six months of treatment, but this study found significant healing in around 12 weeks of treatment by vitamin D group, Calcium group or combination group. Further studies might help to determine whether shorter course are actually sufficient. But whatever the duration of therapy adequate vitamin D and calcium intake should be ensured after treatment.

Limitations

This is a single center study having small sample size. Diet of the study population cannot be ruled out on the outcome of this research.Serum vitamin D level could not be determined due to lack of facilities.

Conclusion

Combination use of vitamin D and calcium in the treatment of nutritional rickets is more effective than prescribing either vitamin D or calcium alone.

Recommendation

Vitamin D along with Calcium may be given for effective treatment of nutritional rickets. Further multicentric studies are needed to find out most effective treatment of nutritional rickets in our country.

Authors' contribution: FY conceived and designed the analysis. FY, FC, MC, TC collected data. FY, FJC performed statistical analysis. FY, FY did interpretation of the results. MH supervised the research. FY, FC wrote the manuscript. All authors provided critical feedback and helped to shape the research, analysis and manuscript.

Conflict of interest: Nothing to declare.

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