International Journal of Contemporary Pediatrics
Haque M et al. Int J Contemp Pediatr. 2025 May;12(5):773-778
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20251097

Original Research Article

Efficacy of vitamin D therapy for resolution of pain symptoms in growing pain children with hypovitaminosis D

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Received: 20 March 2025
Accepted: 15 April 2025

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ABSTRACT

Background: Growing pain (GP) is the most common cause of recurrent musculoskeletal pain in children. GP has association with vitamin D deficiency. To evaluate the efficacy of vitamin D treatment on the resolution of pain symptoms in children having GP with hypovitaminosis D.
Methods: A Prospective open label interventional study was conducted in outpatient department (OPD), Department of Pediatrics, Bangabandhu Sheikh Mujib Medical University, Bangladesh. Children with GP defined by Evans criteria (2008) along with hypovitaminosis D were selected as cases. Initially, serum vitamin D (25(OH)D) and calcium level were measured and pain severity was assessed using Wong Baker Faces Scale. Then 2000 IU/day vitamin D3 was given orally for at least 12 weeks. Serum vitamin D and calcium level along with pain severity assessment were done again to observe the changes after vitamin D therapy.
Results: Total 30 children with GP and hypovitaminosis D were included in this study. Initially, vitamin D deficiency and insufficiency were found in 93.33% and 6.66% children respectively, whereas after vitamin D therapy, majority (70%) of children had achieved normal vitamin D level. Before vitamin D therapy, 43.33% and 53.33% patients had severe and moderate pain, while after therapy, majority (70%) had only mild pain. Mean pain severity score was also significantly decreased after vitamin D therapy.
Conclusions: Vitamin D therapy among the children with growing pains significantly increased the serum vitamin D (25(OH)D) levels and resulted in a significant resolution of pain symptoms, thus improving the quality of life.

Keywords: Growing pain, Vitamin D, Wong baker faces scale

INTRODUCTION

Growing pain (GP) is a well-known clinical entity and most common form of episodic childhood musculoskeletal pain.[1] Growing Pain was first described by French physician Marcel Duchamp.[2] The prevalence of GP has been reported from 1928 and it ranges from as little as 2.6% to 49% of children.[3] Oster found that as many as 15% of school-age children have occasional limb pain.[4] Evans and Scutter in a very large community study in Australia reported a prevalence of 37% in children aged 4–6 years.[3] Haque et al, found 19.3% of Bangladeshi school children aged 6-12 years had growing pain.[5] Few studies have been done to elucidate the cause and pathogenesis of growing pain. The proposed causes of GP according to Uziel et al, and Hashkes et al, are low pain tolerance, over use, low bone strength density, mechanical strains due to flat foot with mild outward turning of back of foot, blood perfusion change, family environment, stress and psychological disposition.[6]

GP has typical clinical features it is usually non-articular, site is located in the shins, calves, thighs or popliteal fossa and GP is almost always bilateral. The pain usually occurs in the evening or at night with pain intensity varying from mild to very severe. The duration ranges

from minutes to hours. Children feel better when they're held, massaged. It almost always resolves by morning. There are no objective signs of inflammation on physical examination.[7] Otherwise healthy children are most commonly affected by growing pain between the ages of 4 and 12 years, but they may also occur in younger age groups.[1] Laboratory test results are generally normal.8 There is no single diagnostic test for growing pain and as a result, it continues to be diagnosed on the basis of both inclusion and exclusion criteria. Most recently, Evan 2008 has proposed diagnostic criteria for growing pain which are currently accepted worldwide.[3]

It was postulated that GP has association with vitamin D (25OH-vit D) deficiency. Vitamin D is a fat-soluble vitamin that maintain normal calcium homeostasis. Vitamin D increases the total intestinal absorption of calcium and phosphorus from 10-20% and 60% to 30-40% and 80%, respectively. In the setting of hypovitaminosis D, serum level of calcium is first to fall, but phosphorus level is maintained within the normal range. This hypocalcemia then leads to secondary hyperparathyroidism, resulting in an increased serum level of 1, 25 dihydroxycholecalciferol, normalization of serum calcium and a fall in plasma phosphorus level.

This homeostasis is achieved by PTH-induced bone re-sorption, which also increases the serum level of alkaline phosphatase. This condition, if left untreated, eventually leads to exhaustion of bone stores and recurrence of hypocalcaemia.[9] A study done at OPD in a tertiary care hospital in Northern India found that 100% children with GP had hypovitaminosis D, 91.1% of them being deficient.[10] A normal vitamin D status seems to be protective against musculoskeletal disorders (muscle weakness, falls and fractures), infectious disease, autoimmune disease, cardiovascular disease, types 1 and 2diabetes mellitus, several types of cancer, neurocognitive dysfunction and mental illness.[11,12]

An association between the vitamin D level and chronic pain conditions has been described; the patients' pain condition improved with vitamin D supplementation.[13,14] A study conducted by Insaf AI in Iraq showed that majority (62.9%) of GP patients had moderate pain followed severe pain (37.1%).[15] Morandi et al, in an Italian study observed significant pain improvement after 3 months of vitamin D supplementation with an increase in serum Vitamin D level which indicated an indirect relationship between vitamin D deficiency with severity of GP in children.[16]

In our country there are no studies available highlighting the improvement of pain symptoms after vitamin D supplementation in children of growing pain with vitamin D deficiency. The aim of this study is diagnosis of growing pain in children with unexplained limb pain and estimation of serum level of vitamin D, calcium in children with GP to determine the relationship between vitamin D deficiency and GP. We will also assess whether there is resolution of pain symptoms and improvement of vitamin D level with vitamin D therapy.

METHODS

This was a Prospective open label interventional study conducted at the paediatric rheumatology follow up clinic of Bangabandhu Sheikh Mujib Medical University (BSMMU), from March 2020 to August 2021. Seventy children aged 6-12 years, fulfilling the Evans criteria3 of growing pain were enrolled in this study. Children with any systemic illness, rheumatologic disorders and children who had taken vitamin D, calcium, steroid or any other DMARD within 3 months were excluded from the study. The study was performed by ethical standards stated in the 1964 declaration of Helsinki and its later amendments. Informed written consent was obtained from parents and institutional review board clearance certificate (No. BSMMU/2021/6319, Date: 8/7/2021) was taken before enrolment of the study. Demographic variables, characteristics of growing pain and serum vitamin D status were recorded in a predesigned questionnaire.

Serum 25 (OH) D was determined by chemiluminescent microparticle immunoassay (CMA) technique using SIEMENS ADVIA centaur XPT in laboratory of National Institute of Nuclear Medicine and Allied Science (NINMAS), BSMMU. Depending on their vitamin D level, patients were classified into 3 categories: levels<20 ng/ml as Vitamin D deficiency; levels 20 to 30 ng/ml as Vitamin D Insufficiency and levels more than 30 ng/ml as Vitamin D sufficiency.[15] Both the vitamin D insufficiency and deficiency groups were considered as Hypovitaminosis D.

Serum calcium was measured by CMA method with the reagent Glycine buffer OCPC/8-Quinolinol using the machine SIEMENS (Dimension ExL automated biochemistry analyzer) in laboratory of NINMAS, BSMMU. To assess pain intensity, Wong–Baker Faces Pain Rating Scale was used in this study.[11] It included a horizontal line of 6 hand-drawn faces, scored from 0 to 10, that ranged from a smiling face on the left to a crying face on the right (hardly noticeable pain versus strongest conceivable pain). Pain severity according to Faces Pain Rating Scale score was interpreted as 'No pain' score 0, 'Mild pain' score 1-3, 'Moderate pain' score 4-6 and 'Severe pain' score 7-10.16 (Figure 1). Parents and older patients were asked to look at the faces scale and select the face which resembled the pain intensity of the patient.[16] Assessment score was recorded in the pre-designed questionnaire.

After 12 weeks of vitamin D treatment, repeat measurements of serum vitamin D along with calcium were done in order to check whether the vitamin D dose was effective for resolution of pain. Pain severity after 12 weeks of vitamin D therapy was evaluated again to observe the change in pain intensity. Numeric data were

expressed as mean±standard deviation and median (range) when appropriate. Qualitative data was expressed as frequency and percentage. Appropriate statistical test (Chi-square test, t test) was applied for data analysis. The 25(OH)D levels and pain severity scores before and after oral vitamin D administration were compared with a paired Student's t test. Statistical analysis was performed by SPSS (statistical program for social science) for version 22. A p value of<0.05 was considered as statistically significant.

RESULTS

A total of 30 children with along with hypovitaminosis D attending at outpatient department (OPD), Department of Pediatrics, Bangabandhu Sheikh Mujib Medical University, Bangladesh during study period were included as cases in this prospective open label interventional study. Table 1 demonstrated demographic data of children with GP among 30 cases. Age range was from 6-12 years. 60% (18) of total cases belonged to 6 years to less than 10 years, whereas rests of the cases were in 10 to 12 years age group. Two third of the children were female 19 (63.33%), one third 11 (36.64%) were male. Male female ratio was 1:1.7. Regarding residence of the patients, 76.66% came from urban area and 23.33% were from rural area.

Our study observed that overweight and obesity were present in 7 (23.33%) and 5 (16.66%) cases respectively. Over-activity was found in 60% (18) of cases. 53.33% (16) of children with GP had family history (Table 2). Table 3 showed the vitamin D status among GP children before and after vitamin D therapy. Before therapy 93.33% (28) and 6.66% (2) children with GP had vitamin D deficiency and insufficiency respectively. No child was found in vitamin D sufficient group. After vitamin D therapy, 70% (21) children had normal level of vitamin D followed by 16.66% (5) and 13.33 (4) children were in vitamin D deficient and insufficient group.

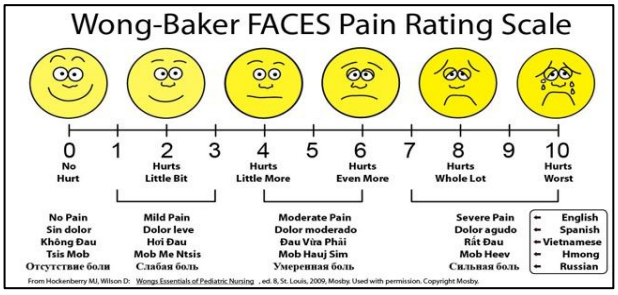

Figure 1: Wong-Baker faces pain rating scale.

In this study we found that before vitamin D therapy, 43.33% (13) and 53.33% (16) patients had severe and moderate pain intensity respectively according to facial pain scale. After vitamin D therapy, most of the patients 70% (21) patients had only mild pain followed by 16.66% (5) moderate pain, 10% (3) patients had moderate pain and 3.3% (1) had complete resolution of pain (Table 4). Table 5 demonstrated that the mean value of vitamin D before and after treatment was 13.197 ng/ml and 32.84 ng/ml. Comparison of serum vitamin D level between these two groups were statistically significant and p value was<0.00001. There was no significant difference regarding mean serum calcium level. Mean pain severity score was significantly reduced after vitamin D therapy (p <0.00001).

Table 1: Demographic data of children with growing pain (n=30).

Data	Frequency	
	Absolute (N)	**(%)**
Age (years)		
6 to<10	18	60
≥10 to 12	12	40
Gender		
Male	11	36.66
Female	19	63.33
Address		
Urban	23	76.66
Rural	7	23.33

Table 2: Frequencies of different risk factors among children with growing pain (N=30).

Risk factors	Frequency	
	Absolute (N)	**(%)**
Overweight (BMI: 85th- <95thcentile)	7	23.33
Obesity (BMI ≥95th centile)	5	16.66
Over activity (>3 hours)	18	60
Family history	16	53.33

Table 3: Frequencies of vitamin D status among children with growing pain before and after vitamin D therapy (n=30).

Biochemical parameter		Frequency			
		Before treatment		After treatment	
		Number (N)	(%)	Number (N)	(%)
Serum 25-(OH)D (ng/ml)	Deficiency<20	28	93.33	5	16.66
	Insufficiency 20-29.9	2	6.66	4	13.33
	Sufficient ≥30	0	0	21	70

Table 4: Pain severity score in growing pain children (n=30).

Severity of pain (Score in Facial pain scale)	Frequency			
	Before treatment		After treatment	
	Absolute (N)	(%)	Absolute (N)	(%)
No pain (0)	0	0	1	3.33
Mild pain (1-3)	1	3.33	21	70
Moderate pain (4-6)	16	53.33	5	16.66
Severe pain (7-10)	13	43.33	3	10

Table 5: Comparison of mean value of serum vitamin D including other biochemical values and pain severity score before and after vitamin D therapy (n=30).

Variable	Before treatment	After treatment	P value
Serum 25 (OH)D (ng/ml)	13.197	32.84	<0.00001*
Serum calcium (mg/dl)	9.2	9.24	0.82332ns
Pain severity score	07	3.1	<0.00001*

P value obtained by paired t-test, *=significant, ns=not significant

DISCUSSION

Recurrent limb pain, termed as growing pains constitute the most frequent cause of musculoskeletal pain in children.[16] Nonspecific musculoskeletal pain has been widely linked to vitamin D deficiency in otherwise healthy children.[11,17] Vitamin D deficiency and insufficiency is a very common health problem among children in Bangladesh. Growing pain could be a manifestation of vitamin D deficiency in children and most of the children with growing pain have vitamin D deficiency.[18] This study aimed to evaluate the efficacy of vitamin D [25(OH)D] treatment on the resolution of pain symptoms in children having growing pain (diagnosed using Evan′s criteria) with hypovitaminosis D.

In our present study, age distribution of growing pain children was between 6-12 years. Highest numbers of cases were found in 6 to less than 10 years age group. Haque et al, in a Bangladeshi study observed similar findings in their study.[19] They found about 63% of growing pain children were between 6 to<10 years age group. A study conducted by Ali et al, found 73.3 % cases were in more than 10 to 12 years, which is much higher than our study findings.[20] These variations in age distribution are due to delayed diagnosis, wrong diagnosis and also depends upon the residence of patients (Urban or rural), awareness of treating physician.

In this current study, girls were found to be predominant in the GP children. This finding is consistent with the Turkish study by Vehapoglu et al, (2015), where 56.6% of the GP cases were girls.[21] Few studies such as, community study done by Haque et al, (2016) and a recent study by Ali et al, (2022) showed male preponderance.[5,20] Our study was done in a tertiary center of capital Dhaka of Bangladesh, here both male and female child usually get attention. But at rural area, male child usually gets more attention than female.

Several risk factors were found among children with growing pains such as overweight or obesity, over activity and family history of growing pain. In the current study 40% of GP cases were found to be either overweight or obese. A study done by Haque et al, (2016) also found one third of GP cases were overweight or obese.[5] Genetic component play a role in the pathogenesis of GP.[3] In this study more than fifty percent children had family history which support the Oster's findings.[22] In our study all children with GP had hypovitaminosis D were enrolled as cases. After enrollment vitamin D supplementation was given and vitamin D status was observed after supplementation.

A study done by Sharma et al, in a tertiary hospital of northern India found that 100% children with GP had hypovitaminosis D.[10] A Bangladeshi study done by Haque et al, found 92% of GP children had hypovitaminosis D.[5] These findings were similar with observations in our study which indicates that children with GP were predominantly vitamin D deficient.

Morandi et al, evaluated 33 children with GP. They found mean 25(OH)D level of 15± 6.9 ngm/ml. They found that vitamin D supplementation leads to a significant increase in the 25(OH)D level that was associated with significant resolution of pain symptoms.[16] In our study, after treatment 70% of GP children became vitamin D sufficient from hypovitaminosis status. Mean vitamin D level was significantly increased from 13.197 to 32.84 ngm/ml after treatment, which was statistically significant (P <0.00001). These findings are similar with the Morandi et al.[16] Here we could not perform a randomized controlled trial because children with GP had hypovitaminosis D. So, it would be unethical to withhold the vitamin D therapy.

In our study we assessed pain intensity of GP children by Wong-Baker Faces Pain Rating Scale. Before treatment approximately 90% of children had moderate and severe intensity pain. After therapy pain intensity was decreased, 70% children had only mild symptoms. These findings had similarity with the study done by Vehapoglu et al, where after vitamin D supplementation they observed a significant reduction in pain intensity in children with GP.[21]

After 3 months of vitamin D therapy, we detected a significant reduction in pain intensity from severe to mild pain, which suggests vitamin D might alleviate the symptoms of growing pain.

We believe that our study is the first to examine the efficacy of vitamin D treatment in children with growing pain using a visual analogue scale (VAS). Dhanani et al, used VAS to determine the difference in pain associated with changes in quality of life in children with musculoskeletal pain. Here author concluded that the VAS can be accepted as a valid and reliable method of assessing pain in pediatric population.[23]

CONCLUSION

In this study, vitamin D therapy among the children with growing pains significantly increased the 25(OH) D levels and caused a significant resolution of pain symptoms. So these findings could suggest that in GP children monitoring of 25(OH)D levels and when indicated, supplementation of oral vitamin D help to restore pain intensity. Thereby reduction of pain leads to an improved quality of life.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Haque M, Ali MA, Islam MM, Islam MI, Talukder MK. Efficacy of vitamin D therapy for resolution of pain symptoms in growing pain children with hypovitaminosis D. Int J Contemp Pediatr 2025;12:773-8.