Tropical Journal of Pharmaceutical Research July 2024; 23 (7): 1135-1140
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v23i7.12

Original Research Article

Efficacy of oral calcium carbonate and vitamin D3 granules for the management of pains in growing limbs in children

Yibing Wang, Jian Cui, Nan Zhang, Xuteng Zhang, Zhengqiang Li, Xinghui Zheng, Jianli Bu

Department of Orthopedics, Bethune International Peace Hospital, Shijiazhuang City 050000, China

For correspondence:* ***Email:* *shun15971@163.com*

Sent for review: 6 August 2023 *Revised accepted: 29 June 2024*

Abstract

Purpose: *To investigate the therapeutic efficacy of calcium carbonate and vitamin D3 granules in bone density and growing limbs in children.*
Methods: *One hundred children with pains in growing limbs were recruited as the study group, juxtaposed with a blank group comprised of 100 healthy children with no pains. Both groups underwent physical examinations at Bethune International Peace Hospital, Shijiazhuang City, China during the study period. Children in the study group were further randomized into treatment group (n = 50) which received orally administered calcium carbonate (500 mg) and vitamin D3 granules (35 µg) once daily for 3 months and control group (n = 50) without treatment intervention. Bone density, pain severity, serum 25-hydroxyvitamin D (25-(OH)D), calcium, and phosphorus levels were determined in all groups.*
Results: *There was no significant difference in serum calcium, phosphorus, and bone density Z-scores in the study and control groups ($p > 0.05$). Also, the presence of pains in growing limbs of children was associated with significantly lower serum levels of 25-(OH)D ($p < 0.05$), but treatment with calcium carbonate and vitamin D3 granules significantly ameliorated pain ($p < 0.05$). After treatment, children who received calcium carbonate and vitamin D3 granules exhibited significantly higher bone density Z-scores, with higher scores observed in those with effective treatment outcomes compared to those with ineffective outcomes ($p < 0.05$).*
Conclusion: *Pains in growing limbs of children are associated with serum 25-(OH)D levels. Oral administration of calcium carbonate and vitamin D3 granules significantly alleviates the severity of pains and improves bone density. Further studies using larger patient populations and multi-racial centers will be needed to consider potential factors such as genetic and environmental that may have an impact on the study outcomes.*

Keywords: *Pains in growing limbs, 25-(OH)D, Calcium carbonate, Vitamin D3 granules, Bone density*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, Web of Science, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Pains in growing limbs in children are intermittent and localized pains that predominantly occur at night. The pain is mostly domiciled in the lower limb without any direct or apparent causes, with a global prevalence of approximately 10 - 20 % among children [1]. Despite an elusive mechanism, this non-inflammatory pain has been shown to be associated with psychological

(stress and anxiety, emotional sensitivity, sleep disturbances) and anatomical factors (muscle fatigue, musculoskeletal imbalances, rapid growth), excessive use of growing limbs, and low pain thresholds [2]. The duration, frequency, and severity of growing pain episodes vary widely, and it is diagnosed based on medical history and physical examination, without the need for laboratory tests [3].

In most cases, pains in growing limbs of children are benign and tend to self-limit when approaching adolescence, with virtually no risks associated with any further serious illnesses [4]. However, psychological outcomes such as anxiety arising from this syndrome are not neglected, so proper knowledge and understanding of pains in growing limbs of children are essential in mitigating the incidence of harmful psychological effects [5]. A systematic review indicated that low pain thresholds, decreased bone density, vitamin D deficiency, and psychological factors are potential mechanisms for the onset of pains in growing limbs of children [6]. Vitamin D is an essential component of skeletal and mineral metabolism, a trace element necessary for accelerating calcium absorption in the intestines, and crucial for normal growth plate calcification and bone mineralization. It plays a significant role in homeostasis of calcium and phosphorus, being essential for bone mineralization, skeletal growth, and overall bone health [7]. Insufficient vitamin D leads to reduced calcium absorption and serum calcium levels, triggering secondary hyperparathyroidism, thereby increasing bone resorption and serum alkaline phosphatase (ALP) levels [8].

Study by Qamar *et al* [9] among 100 children with pains in growing limbs revealed that 22 cases had insufficient vitamin D (levels between 20 - 30 ng/mL), while deficiency was seen in 72 cases (levels below 20 ng/mL) [9]. In adults, studies have described an association between vitamin D levels and chronic pain conditions, with a reduction in pain following vitamin D supplementation [10]. Thus, this study investigated the effectiveness of vitamin D3 supplementation in mitigating the severity of pains in the growing limbs of children.

METHODS

Baseline characteristics

A total of 100 children with pains in growing limbs admitted to Bethune International Peace Hospital, Shijiazhuang City, China from January 2020 to January 2022 were recruited into study group juxtaposed with a blank group consisting of 100 healthy children. Children in both groups underwent physical examinations at the hospital during the same period. Study group were further randomized into treatment (n = 50) and control groups (n = 50). The treated group received calcium carbonate and vitamin D3 granules while control group (n = 50) received no treatment intervention. This study was approved by the Ethics Committee of the Hospital (approval no. 2022-090-22), and conducted according to the guidelines of the Declarations of Helsinki [11]. Informed consent was obtained from the parents or guardians of the children, who signed informed consent forms.

Inclusion criteria

Children ≤ 14 years, meeting the diagnostic criteria for pains in growing limbs of children (intermittent, non-articular leg pain that typically occurs later in the day or at night and can self-resolve) [12], no significant abnormalities observed on physical examination, no signs of inflammation, symptom duration ≥ 6 months, no abnormalities in erythrocyte sedimentation rate, rheumatoid factor, and other tests.

Exclusion criteria

Children > 14 years, > 6 months duration of symptoms, lower limb pain caused by other conditions such as trauma, infection, and bone tumors, interruption, non-compliance, or loss to follow-up during treatment.

Interventions

The treatment group received one sachet of calcium carbonate and Vitamin D3 granules (Beijing Zhendong Kangyuan Pharmaceutical Co., Ltd., NMPA approval no. H20090334), once daily orally with each sachet containing 500 mg of calcium and 35 µg of vitamin D for 3 months. During treatment, outdoor activities and exposure to sunlight for approximately 2 h were encouraged, and attention was given to maintaining a balanced diet. Control group was advised to engage in appropriate outdoor activities and exposure to sunlight without treatment intervention.

Evaluation of parameters/indices

Serum 25-hydroxyvitamin D, calcium and phosphorus levels

A total of 3 mL morning fasting elbow venous blood was collected from patients after treatment and was centrifuged for 10 min to obtain the

supernatant, which was then stored at -20 °C for further analysis. Serum 25-(OH)D levels were measured using liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) according to the manufacturer's specifications. Blood calcium was determined using the azo-molybdate method, and blood phosphorus was determined using the phosphomolybdate method.

Measurement of bone density

Bone density at the distal one-third of the left forearm radius of the children was measured using a BMD-1000 ultrasound bone densitometer [13].

Pain severity and clinical efficacy

After 3 months of treatment, the Visual Analog Scale (VAS) score [14] was employed to assess pain severity, and the VAS reduction rate was used to evaluate clinical efficacy. A VAS score of 0 indicates no pain, while a score of 10 represents the most severe and unbearable pain. The VAS reduction rate (VR) was obtained using Eq 1 [14].

$$VR\ (\%) = \{VAS_{pre} - VAS_{post})/VAS_{pre}\}100 \ldots (1)$$

Where VAS_{pre} is pretreatment VAS, and VAS_{post} is post-treatment VAS

Clinical cure [14] was defined as a VAS reduction rate ≥ 75 %, significantly effective as a VAS reduction rate of 75 % to 50 %, and ineffective as a VAS reduction rate < 50 %. The effective rate (ER) was calculated using Eq 2.

$$ER = \{(Cure + SE)/N\}100 \ldots\ldots\ldots\ldots (2)$$

Where SE is significantly effective and N represents the total number of cases

Statistical analysis

Data were analyzed using Statistical Packages for Social Sciences (SPSS 22.0 software, IBM, Armonk, NY, USA). Count data were represented as percentages (%) and compared using Chi-squared test. Count data were expressed as mean ± standard deviation (SD) and analyzed using *t*-test. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

There was no statistical difference in baseline characteristics between the two groups ($p > 0.05$; Table 1).

Blood calcium and phosphorus levels

Before treatment, concentrations of blood calcium and phosphorus were 2.41 ± 0.22 mmol/L and 2.15 ± 0.26 mmol/L respectively in study group. Concentrations of blood calcium and phosphorus were 2.33 ± 0.29 and 2.09 ± 0.22 mmol/L respectively in the control group. Children either with or without pains in growing limbs had similar levels of blood calcium and blood phosphorus concentration ($p > 0.05$; Figure 1).

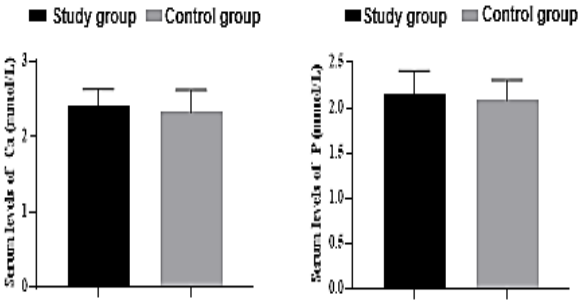

Figure 1: Blood calcium and phosphorus levels after treatment

Serum 25-(OH)D levels and bone density

In the study group, the concentration of 25-(OH)D was 21.69 ± 3.26 mmol/L and the bone density Z-score was 0.96 ± 0.32. The concentration of 25-(OH)D was 32.21 ± 6.32 mmol/L and the bone density Z-score was -0.87 ± 0.29 in control group.

Table 1: Baseline characteristics

Characteristic	Study	Control	χ2/t	*P*-value
Gender (n)			1.648	0.199
Male	39	48		
Female	61	52		
Age (years)	8.22±2.01	7.93±1.92	1.043	0.298
Height (cm)	139.8±18.2	142.2±17.63	0.947	0.345
Weight (kg)	29.33±4.96	30.12±5.63	1.053	0.294
BMI (kg/m^2)	15.23±3.25	15.96±3.47	1.535	0.126

Children with pains in growing limbs exhibited significantly lower 25-(OH)D levels than those without this syndrome ($p < 0.05$), while bone density was similar between the two groups of children ($p > 0.05$).

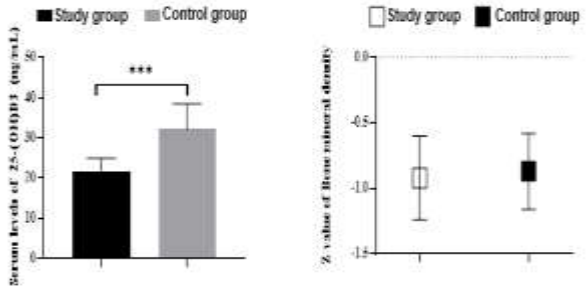

Figure 2: Serum 25-(OH)D and bone mineral density after treatment. ***$P < 0.001$ compared to control group

Clinical efficacy of calcium carbonate and vitamin D3 granules

In the treatment group, there were 24 cases of clinical cure, 17 significantly effective cases, and 9 ineffective cases, with an overall effective rate of 82 % (41/50). In the control, there were 8 cases of clinical cure, 16 significantly effective cases, and 26 ineffective cases, with an overall effective rate of 52 % (26/50). Calcium carbonate and vitamin D3 granules provided significant reduction in pain severity in growing limbs of children ($p < 0.05$; Table 2).

Relationship between efficacy and bone density

Based on clinical efficacy, patients were divided into effective and ineffective groups. Differences in bone density before and after treatment were compared between the two groups. The results revealed that children who received calcium carbonate and vitamin D3 granules exhibited significantly higher bone density Z-scores, with higher scores observed in those with effective treatment outcomes compared to those with ineffective outcomes ($p < 0.05$).

DISCUSSION

Pains in growing limbs of children are a common pediatric condition, with a high global prevalence among children between the ages of 2 and 12 years. It is also the prevailing cause of chronic leg pain in children and adolescents. A study assessed 345 children and adolescents with chronic leg pain and revealed that 300 individuals (87 %) were ultimately diagnosed with pains in growing limbs [12]. In most cases, pains in the growing limbs of children resolve without need for treatment during adolescence and do not lead to adverse outcomes [13]. However, recurrent episodes of pain may result in compromised sleep quality, psychological well-being, and social interactions in children [14]. Results of the current study found no significant alterations in bone density, blood calcium, or blood phosphorus levels in children after being diagnosed with pains in growing limbs.

The specific etiology underpinning pains in growing limbs of children remains unclear, but anatomical conditions, bone metabolism, psychological factors, and intensity of physical activity are contributing factors [15]. Skeletal growth is a continuous remodeling process, involving the resorption of old bone by osteoclasts and the formation of new bone by osteoblasts. Blood calcium and phosphorus levels may, to some extent, indicate bone metabolism. Low blood calcium levels, also known as hypocalcemia, may suggest impaired bone metabolism, as it could indicate inadequate calcium absorption or increased calcium loss from the bones.

Table 2: Clinical efficacy of calcium carbonate and vitamin D3 granules (n=50)

Group	Clinical cure	Effective	ineffective	Total effective rate
Treatment	24	17	9	41(82%)
Control	8	16	26	26(52%)
χ^2				10.18
P-value				0.001

Table 3: Relationship between clinical efficacy and bone mineral density

Group	n	Before treatment	After treatment
Effective group	67	-0.92±0.26	-0.77±0.17
Ineffective group	33	-0.97±0.28	-0.88±0.19
T-value		0.882	2.926
P-value		0.380	0.004

Similarly, low blood phosphorus levels, known as hypophosphatemia, may be a sign of impaired bone metabolism, as phosphorus is an essential nutrient for bone formation. On the other hand, high blood calcium levels, known as hypercalcemia, or high blood phosphorus levels, known as hyperphosphatemia, may indicate increased bone metabolism.

Elevated levels of these minerals in the blood may be a result of increased bone resorption, where calcium and phosphorus are released from the bones into the bloodstream. Currently, there is an ongoing controversy regarding the relationship between blood calcium and phosphorus levels with pains in growing limbs of children, on which no high-quality studies are available [16]. A cross-sectional study conducted on elementary and middle school students in Turkey found that diagnosed cases of pains in growing limbs of children had blood calcium and phosphorus levels within the normal range, consistent with the results of this study [17]. Serum levels of 25-(OH)D in children with pains in growing limbs were significantly lower than those in healthy children. Vitamin D is a vital fat-soluble steroid derivative necessary for maintaining normal physiological functions in the body, particularly for skeletal health. Vitamin D deficiency in childhood may affect the growth and development of the skeleton. 25-(OH)D is the primary form of vitamin D in the body and is relatively stable over an extended period, with minimal influence from the body's regulation [18]. The correlation between vitamin D and skeletal health has been substantiated by numerous studies, with significant associations between 25-(OH)D levels and outcomes related to skeletal health such as rickets, falls, and bone density [19].

A cohort study by Morandi *et al* [19] revealed a correlation between the intensity of pains in growing limbs of children and levels of vitamin D and bone density [20]. A study involving 120 Turkish children aged 4 to 12 years with pains in growing limbs revealed that vitamin D deficiency might be a contributing factor, and supplementation of vitamin D would reduce the intensity of discomfort experienced. A total of 61.6 % of children had 25-(OH)D levels < 20 ng/dL, and 25 % had 25-(OH)D levels < 10 ng/dL. Furthermore, after receiving vitamin D supplements for 3 months, pain scores significantly decreased [21]. In this current study, the treatment group received oral administration of Calcium Carbonate and Vitamin D3 granules and achieved similar results. Additionally, this study compared alterations in bone density in children with different clinical outcomes and found better improvement in bone density in the effective group compared to the ineffective group, suggesting a possible relationship between the alleviation of growing pain and increased bone density. However, this would require further investigation.

Limitations of this study

Although this study has presented vital findings, there are still limitations that need to be addressed and improved in future. The limited sample size may affect the representativeness and generalizability of the results. This study employed a cross-sectional design which may limit the ability to observe long-term effects and establish vital findings. Also, reliance on self-report measures may introduce bias or memory distortion challenges. Using more objective and reliable data collection methods, such as objective measurements or long-term follow-ups, may enhance the reliability of the findings.

CONCLUSION

Pains in growing limbs of children have been associated with low serum 25-(OH)D levels. Oral administration of calcium carbonate and vitamin D3 granules increases serum level of 25-(OH)D thus significantly alleviating pain severity, and improving bone density in growing limbs of children. Future studies using larger patient populations and multi-racial centers will be needed to consider potential factors such as genetic and environmental that may have impact on the study outcomes.

DECLARATIONS

Acknowledgements

The study was supported by the Epidemiological investigation of pains in growing limbs in children and their correlation with bone density (no. 20231284).

Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

Open Access

REFERENCES

1. *Khuntdar BK, Mondal S, Naik S, Mohanta MP. Prevalence of growing pains in a general pediatric OPD: A descriptive, observational and cross-sectional study. J Family Med Prim Care 2023; 12: 117-122.*
2. *Mohanta MP. Growing pains: practitioners' dilemma. Indian Pediatr 2014; 51: 379-383.*
3. *Asadi-Pooya AA, Bordbar MR. Are laboratory tests necessary in making the diagnosis of limb pains typical for growing pains in children? Pediatr Int 2007; 49: 833-835.*
4. *Uziel Y, Chapnick G, Jaber L, Nemet D, Hashkes PJ. Five-year outcome of children with growing pains: correlations with pain threshold. J Pediatr 2010; 156: 838-840.*
5. *Walters AS, Gabelia D, Frauscher B. Restless legs syndrome (Willis-Ekbom disease) and growing pains: are they the same thing? A side-by-side comparison of the diagnostic criteria for both and recommendations for future research. Sleep Med 2013; 14: 1247-1252.*
6. *Pavone V, Vescio A, Valenti F, Sapienza M, Sessa G, Testa G. Growing pains: What do we know about etiology? A systematic review. World J Orthop 2019; 10: 192-205.*
7. *Shapses SA, Calvo MS. Health benefits of Vitamin D supplementation: Time to move the spotlight away from bone health in Vitamin D-replete individuals? Am J Clin Nutr 2023; 118: 489-490.*
8. *Atapattu N, Shaw N, Högler W. Relationship between serum 25-hydroxyvitamin D and parathyroid hormone in the search for a biochemical definition of vitamin D deficiency in children. Pediatr Res 2013; 74: 552-556.*
9. *Qamar S, Akbani S, Shamim S, Khan G. Vitamin D levels in children with growing pains. J Coll Physicians Surg Pak 2011; 21: 284-287.*
10. *De Rezende Pena C, Grillo LP, Das Chagas Medeiros MM. Evaluation of 25-hydroxyvitamin D serum levels in patients with fibromyalgia. J Clin Rheumatol 2010; 16: 365-369.*
11. *World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013; 310(20): 2191-2194.*
12. *Piano LP, Golmia RP, Golmia AP, Sallum AM, Nukumizu LA, Castro DG, Scheinberg MA. Diagnosis of growing pains in a Brazilian pediatric population: a prospective investigation. Einstein (Sao Paulo) 2010; 8: 430-432.*
13. *Uziel Y, Chapnick G, Oren-Ziv A, Jaber L, Nemet D, Hashkes PJ. Bone strength in children with growing pains: long-term follow-up. Clin Exp Rheumatol 2012; 30: 137-140.*
14. *Karcioglu O, Topacoglu H, Dikme O, Dikme O. A systematic review of the pain scales in adults: which to use? Am J Emerg Med 2018; 36(4): 707–714.*
15. *Vasilopoulou M, Spathis A, Myriokefalitakis N, Zaferopoulou F, Paspati I, Tsolia M. Development of a screening tool for children's growing pains: validation, reliability control and clinical evaluation. Turk J Pediatr 2015; 57: 467-474.*
16. *Friedland O, Hashkes PJ, Jaber L, Cohen HA, Eliakim A, Wolach B, Uziel Y. Decreased bone speed of sound in children with growing pains measured by quantitative ultrasound. J Rheumatol 2005; 32: 1354-1357.*
17. *Akal F, Batu ED, Sonmez HE, Karadağ Ş G, Demir F, Ayaz NA, Sözeri B. Diagnosing growing pains in children by using machine learning: a cross-sectional multicenter study. Med Biol Eng Comput 2022; 60: 3601-3614.*
18. *Li H, Wang B, He L, Tao R, Shang S. Application of bone metabolic parameters in the diagnosis of growing pains. J Clin Lab Anal 2022; 36: e24184.*
19. *Cranney A, Horsley T, O'Donnell S, Weiler H, Puil L, Ooi D, Atkinson S, Ward L, Moher D, Hanley D, et al. Effectiveness and safety of vitamin D in relation to bone health. Evid Rep Technol Assess (Full Rep) 2007; 1-235.*
20. *Morandi G, Maines E, Piona C, Monti E, Sandri M, Gaudino R, Boner A, Antoniazzi F. Significant association among growing pains, vitamin D supplementation, and bone mineral status: results from a pilot cohort study. J Bone Miner Metab 2015; 33: 201-206.*
21. *Vehapoglu A, Turel O, Turkmen S, Inal BB, Aksoy T, Ozgurhan G, Ersoy M. Are growing pains related to vitamin D deficiency? Efficacy of vitamin D therapy for resolution of symptoms. Med Princ Pract 2015; 24: 332-338.*