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Clinical Trial

Involvement of bone-specific alkaline phosphatase and procollagen I carboxy-terminal propeptide as predictors of early fracture risk in Chinese children with juvenile osteoporosis

Yu Wang, Jingxin Zhao, Lingwei Kong and Yu Jin

Trauma Department of Orthopedics, Affiliated Hospital of Chengde Medical College, Chengde, Hebei 067000, P. R. China.

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Abstract

This clinical trial was designed to understand whether the children with juvenile osteoporosis receiving tablet containing vitamin D and calcium had lower incidence of bone fracture compared to the children receiving a diet rich in calcium, vitamin D, and protein. We assessed whether plasma levels of bone-specific alkaline phosphatase (BSAP) and procollagen I carboxy-terminal propeptide levels (PIPC) could be used as predictors of early bone fracture in children. A total of 120 children of either gender with a juvenile osteoporosis were enrolled and randomized (1:1 ratio) to receive tablet containing vitamin D and calcium (n=60) or diet rich in calcium, vitamin D, and protein (n=60), and undergone follow-up for up to 3 years. Blood sample was collected and BSAP and PIPC levels were measured. The results suggested that therapeutic intervention (vitamin D and calcium) does not predict bone fracture in children. However, correlations analysis revealed that the decreased level of BSAP and PIPC were associated with higher incidence of fracture. The results suggest that the low levels of BSAP and PIPC cause increase susceptibility of fracture among children with juvenile osteoporosis.

Introduction

Osteoporosis is one of the leading causes of morbidity and becoming a major public health problem worldwide and its prevalence is increasing. This morbidity burden has considerable medical, social and financial implications due to the fractures associated with the disease. It eventually results in fractures of the spine, hip, forearm, and other bones not typically susceptible to fracture in young healthy individuals in the absence of significant trauma (Alswat, 2017). Osteoporosis is a well-established clinical worldwide problem for adults. Instead, osteoporosis in children and adolescents is rather new and increasingly recognized with certain unique diagnostic and clinical challenges (Khoshhal, 2011). In fact, some researchers suggested that osteoporosis seen later in life may originate during childhood or adolescence years. Osteoporosis is an important public health problem in China although the prevalence of osteoporosis remains low compared to that in the white population (Wang et al., 2009; Zhang et al., 2014; Tsai et al., 1996).

It has been reported that the higher levels of bone formation and resorption markers were significantly associated with higher bone mineral density (BMD) loss. In clinical studies, it appears that markers of bone resorption may be useful predictors of fracture risk and bone loss. The association of markers of bone resorption with hip fracture risk in adults is independent of BMD, but a low BMD combined with high bone resorption biomarker may increases the risk of fracture. However,

the predictive value of biomarkers in assessing an individual child has not yet been confirmed (Khoshhal, 2011). Bone turnover markers may have a future role in the clinical management of osteoporosis.

It is not known whether the children with juvenile osteoporosis receiving tablet containing vitamin D and calcium had lower incidence of bone fracture compared to the children receiving a diet rich in calcium, vitamin D, and protein, plays any role in predicting the bone fracture among children with juvenile osteoporosis. Also, it is not known whether plasma levels of bone-specific alkaline phosphatase (BSAP) and procollagen I carboxy-terminal propeptide levels (PIPC) could be used as predictors of early bone fracture in children. We therefore designed this interventional clinical trial to understand whether the children with juvenile osteoporosis receiving tablet containing vitamin D and calcium had lower incidence of bone fracture compared to the children receiving a diet rich in calcium, vitamin D, and protein. We also assessed whether plasma levels of bone-specific alkaline phosphatase (BSAP) and pro-collagen I carboxy-terminal propeptide levels (PIPC) could be used as predictors of early bone fracture in children.

Materials and Methods

In this interventional clinical trial, the children with a juvenile osteoporosis or history of bone fractures were enrolled at Trauma Department of Orthopedics, Affiliated Hospital of Chengde Medical College, China. A total of 138 patients were entered into the screening phase. Of these, a total of 120 Chinese children during January 2012 to December 2016 who were visited in our hospital at the time of their consultation were enrolled and undergone follow-up for up to 3 years. All participants underwent laboratory tests including bone mineral density or any other investigation as required investigator to confirm their eligibility for this trial. All enrolled children were enrolled and randomized to receive tablet containing vitamin D and calcium or diet rich in calcium, vitamin D, and protein, and undergone follow-up for up to 3 years in allocation ration of 1:1.

Blood samples (5 mL) were obtained from each enrolled subjects for estimation of BSAP and PIPC. Blood was collected into a tube containing potassium ethylene-diamine tetraacetic acid (EDTA) and stored at less than 80°C. Venous blood sample of all the recruited subjects was drawn in syringe taking all aseptic precautions between 2 pm to 4 pm. The sample taken was kept in plain vial at room temperature before sending in to laboratory. The sample was tested for serum level of BSAP and PIPC by ELISA kit.

Since this trial was a pilot interventional clinical trial, hence, no formal sample size calculation was performed. However, at least 100 children with juvenile osteoporosis have planned to include in this trial.

Statistical analysis

Correlations between the levels of BSAP and PIPC with the incidences of fracture were done using Pearson's correlation/regression models. Statistical analysis was performed using version 6.2 of GraphPad Prism.

Table I

Demographic and clinical characteristic of Chinese children

Variable	Tablet containing vitamin D and calcium (n=60)	Diet rich in vitamin D, calcium and protein (n=60)
Age in year, mean (SD)	**11.6** (1.1)	**12.7** (1.3)[a]
Female/male, n	22/21	38/19[b]
Children with history of fracture, n (%)	**2** (3.3)	**5** (8.3)[a]
Weight in kg, mean (SD)	**34.5** (1.2)	**33.5** (1.3)[a]
Height in cm, mean (SD)	**144** (1.8)	**148** (1.1)[a]
New fracture incidence during follow-up, n (%)		
Yes	**18** (30)	**22** (36.7)
No	**42** (70)	**38** (63.3)

[a]p>0.05 indicate no statistical significant difference. P value was calculated by Un-paired test; [b]p>0.05 indicate no statistical significant difference. P value was calculated by Chi-square test

Table II

Percentage change in bone-specific alkaline phosphatase (ug/L) and procollagen I carboxy-terminal propep-tide from baseline to endpoint in Chinese children with juvenile osteoporosis

Variable	Subjects with fracture (n = 40) (Median)	Subjects with no fracture (n = 80) (Median)	Effect size (95% Confidence interval of difference)	P values (between group comparison)
Bone-specific alkaline phosphatase				
n	40	80		p<0.001[b]
Baseline (Median)	10.8	12.2	1.36 (0.92-2.62)	
Endpoint (Median)	8.3	15.4	7.01 (5. 2-9.35)	
Within group comparison	p<0.001[a]	p=0.243[a]		
Procollagen I carboxy-terminal propeptide				
n	40	80		p<0.001[b]
Baseline (Median)	110.0	112.0	2 (1.02-3.9)	
Endpoint (Median)	86.0	128.0	42 (32.5- 57.4)	
Within group comparison	p=0.002[a]	p=0.143[a]		

[a]p value was calculated by Mann-Whitney test; [b]p value was calculated by Wilcoxon test

Table III

Relationship between BSAP and PIPC with the incidences of fracture in children with juvenile osteoporosis

Key biomarkers	Fracture incidences (n = 40)	
Key biomarkers	Beta-coefficients	
Bone-specific alkaline phosphatase	-0.8	p<0.005
C-terminal propeptide (PICP) of type-I procolla-gen	-0.5	

n = Total number of subjects. Analysis was performed using Pear-son's correlation/regression models

Results

Of enrolled children, a total of 40 children developed at least 1 bone fracture (33.3%) during 3 year follow-up period, and remaining 80 children did not experienced any fracture. Majority of identified patients were female (female: 60%, male: 40%) with mean (SD) age of 12.2 (1.4) years. Demographic and clinical characteristic of patients are presented in Table I.

Our trial results showed that there is not statistically significant difference in fracture incidence rate between the children who received tablet containing vitamin D and calcium and the children receiving a diet rich in calcium, vitamin D, and protein (Table I). The children who received tablet containing vitamin D and calcium had fracture incidence of 30%, whereas the children who received diet rich in calcium, vitamin D, and protein had fracture incidence of 36.7%. The difference of 6.7% between the two groups was not statistically significant (p<0.561). We also performed subgroup analysis based on the bone biomarker and fracture incidence rate of patients who received calcium and vitamin D as intervention. In this sub-group analysis, it was noted that the levels of BSAP and PIPC were significantly lesser in sub-group who had higher incidence of fracture, irrespective of therapeutic inter-vention (calcium and vitamin D). Correlations analysis revealed that the decreased level of BSAP (median: 8.3 µg/L) and PIPC (median: 86.0) were associated with higher incidence of fracture (Table II and III).

Discussion

This was the first interventional clinical trial to understand whether the children with juvenile osteoporosis receiving tablet containing vitamin D and calcium had lower incidence of bone fracture compared to the children receiving a diet rich in calcium, vitamin D, and protein. Our study results showed that there was no statistical significant difference in incidence of bone fracture between children of both the groups (tablet containing vitamin D [30%] and calcium or diet rich in calcium, vitamin D, and protein [36.7%], with p= 0.561 using Chi-square test as indicated in Table I). We also assessed whether plasma levels of BSAP and PIPC could be used as predictors of early bone fracture in children. Due to high intraindividual and inter-individual variability and large discrepancy in normal values of bone biochemical markers, it is difficult to

recognize the individuals who may be at risk of developing bone trauma/fracture risk (Jensen et al., 1997a; Jensen et al., 1997b). In addition to this, there is a large variability between analytical methods and standard from laboratory to laboratory (Jensen et al., 1997a; Jensen et al., 1997b). Authors have concluded that large biological variability in the biochemical markers of bone turnover make them unsuitable for diagnosis for prediction of future bone loss in individual patients (Jensen et al., 1997a; Jensen et al., 1997b). In this trial, we have used standardized method and performed all the assessment at single laboratory in order to avoid any confounding variables. Correlations analysis revealed that the decreased level of BSAP and PIPC were associated with higher incidence of fracture in the children with juvenile osteoporosis. Our trial results are in consistent with the previous reports which suggested the involvement of BSAP and PIPC in fracture (Bowles et al., 1997; Borys et al., 2001). In contrast to this, another trial results showed that biochemical bone markers are not useful in diagnosing of osteoporosis (Nawawi et al., 2001). This may be due to high variability in response of enrolled patients.

Since the trial was designed as pilot trial and conducted at single center trial in China (limitation of this clinical trial). Therefore, the present findings cannot be generalized to the overall Chinese population. Our trials results encourage for conducting large multi-centric randomized clinical trial in future to generalize the findings of this trial. The hypothesis of this trial for relationship between the levels of BSAP and PIPC with the incidences of fracture was met. Overall, results showed the low levels of BSAP and PIPC causes increase susceptibility of fracture among children with juvenile osteoporosis. Thus, our trial results showed that the levels of BSAP and PIPC are one of the key predictors of early bone fracture in Chinese children with juvenile osteoporosis.

Conclusion

The results of this first pilot interventional clinical trial suggested that therapeutic intervention does not predict fracture risk in children with juvenile osteoporosis. However, the lower levels of BSAP and PIPC can be considered as predictors of fracture risk in children with juvenile osteoporosis.

Ethical Issue

The trial protocol was approved by the Ethics Committee of Chengde Medical College, China, and written informed consent was taken from each trial subjects. All subjects were educated about the trial protocol and the likely benefits to the society.

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Author Info
Yu Jin (Principal contact)
e-mail: JOrieneigi@yahoo.com