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Bone Mineral Density in Epileptic Children Getting Long Term Anti-epileptic Drugs

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Epilepsy is a common chronic neurological disorder with more than half of cases beginning in childhood. Most patients require long-term, and sometimes life-long, therapy with antiepileptic drugs (AEDs). AEDs are associated with significant side effects including radiological evidence of rickets, decreased bone mineral density (BMD), altered bone turnover, and increased risk of fracture.
Aim of the Study: To assess the bone mineral density in epileptic children getting long term anti-epileptic drugs.

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Materials and Methods: This study was conducted in the Saleh Child Development and Disability Management Center (SCDDMC), of the Institute of Child and Mother Health (ICMH) Matuail, Dhaka. A total of 31 childrens age ranged 5-15 years diagnosed as epilepsy on the basis of both clinical examination and investigation (EEG) receiving antiepileptic drugs (AEDS) for at least two years were recruited in this study.

Results: Almost two third (61.3%) children age group were in 5 to 10 years and 12(38.7%) in 10 to 15 years. Around three fourth (74.2%) children were male and 8(25.8%) were female. More than two third (67.7%) children had adequate sun exposure and more than three fourth (77.4%) children got adequate calcium and vit.D rich food. Majority (83.9%) of the patients got phenobarbitone (PB) followed by 17(54.8%) got combination, 13(41.9%) got valproic acid (VPA), 11(35.5%) got Nitrazipum (NTZ). More than one third (38.7%) children got mono therapy, 19(61.3%) got polytherapy. Majority of the children (96.8%) had serum calcium normal. The mean serum calcium was 9.22±0.78 mg/dl. The mean BMD of spine was 0.66±0.14. The mean BMD of neck left femur was 0.66±0.15. The mean BMD of neck right femur 0.66±0.15. More than two third (67.7%) children had low (<-1SD) BMD Z score. Almost two third (60.0%) children had mono therapy showed BMD Z score normal (>-1SD) and 6(28.6%) had BMD Z score low (<-1SD). Almost three fourth (71.4%) children got poly therapy showed low BMD and 4(20.0%) got poly therapy showed normal BMD Z score. No significant association was found between BMD score and type and duration of therapy.

Conclusion: AEDs decreased bone mineral density due to long term use as mono-therapy or polytherapy. The assessment of BMD among children with epilepsy receiving long term AEDs is essential.

Keywords: Epilepsy; anti-epileptic drugs; BMD; bone metabolism.

1. INTRODUCTION

"Epilepsy is a disease characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition. A person is considered to have epilepsy if at least two unprovoked (or reflex) seizures occur greater than 24 hours apart" [1]. "It is a common and chronic neurologic disorder worldwide. The prevalence of epilepsy varies among countries which may be 1.5 in developed countries to 18 per 1000 in Latin America" [2]. "It has been estimated that 80.0% of 50 million people with epilepsy reside in developing countries" [3]. "The risk of having epilepsy at some point in average life span of any individual varies between 2.0% to 5.0%. Some hospital and community based studies from South East Asian countries (SEAR) have reported the incidence of epilepsy from 2 to 10 per thousand population" [4]. "WHO estimates that there are at least 1.5 to 2.0 million people suffering from epilepsy in Bangladesh" [2]. "The incidence and prevalence of epilepsy being higher in poor areas which may be 49 to 225 per 100,000 people per year which poses a huge social and economic burden to the poor. It is very interesting that about half of the total epilepsy population lives in Asia" [3]. "Childhood epilepsy is a great concern to Neurologist. The incidence of epilepsy is high in childhood which decreases in adulthood and can rise again in older age. The first peak occurs in the childhood as well as the young adults; however, another peak age is in old age" [5]. "Epilepsy cases are reported higher in rural area than in urban area especially in developing countries" [6]. "Most patients require long-term and sometimes lifelong therapy with antiepileptic drugs (AEDs). AEDs are associated with significant side effects not limited to radiological evidence of rickets but decreased bone mineral density (BMD), altered bone turnover, and increased risk of fracture" [7]. "Osteopenia is considered a silent disease because bone loss can occur gradually without symptoms. It occurs due to inadequate mineralization of bone" [8]. "Osteomalacia increases the risk of fracture. Bone mineralization begins at birth and plateaus in the third decade of life with subsequent gradual bone loss as a natural process of aging. Many studies reported significant reduction in bone mineral density among children with epilepsy especially those who are receiving poly therapy treatment that is more than single anti-epileptic drug" [9]. "A longitudinal study revealed that use of AEDs leads to accelerated bone loss at the proximal femur in women with epilepsy aged 65 years and older. The authors concluded that, if unabated, bone loss would be sufficient to increase the risk of hip fracture by 29% over 5 years. According to one estimate, there is a risk of bone density decreasing by 1.8% per year with phenytoin (PHT) treatment" [10]. "In addition,

increasing the duration of treatment with antiepileptic drug may increase the risk of osteopenia and fractures" [11]. "Many studies reported that the pathological effects of AEDs start to appear mainly after 5 years of AED treatment" [12,13]. "These observations have increased the demand for better diagnostic and therapeutic tools to address bone health in children including: a laboratory investigation and dual-energy x-ray absorptiometry (DXA)" [14]. "Some studies showed that the fracture rate in epileptic patients is two to six times higher than the observed rate in the general population" [15]. "Previous studies found that fracture risk was higher for hepatic enzyme inducing AEDs such as phenytoin (DPH), carbamazepine (CBZ), and phenobarbital (PB) than non-inducing AEDs, while no significant effect was reported with the new AED and ethosuximide" [16]. "Moreover, the duration of AED treatment, polypharmacy, and gender difference have positive correlation with predicted bone loss" (Oner et al. 2004) [12]. "A large number of biochemical abnormalities affecting bone metabolism had been reported in most of epileptic patients on AEDs. These abnormalities include hypocalcemia, hypophosphatemia, low biologically active vitamin D levels, and increase in parathormone (PTH) levels" [17]. "These effects have been commonly seen with hepatic enzyme-inducing AEDs which increase the catabolism of vitamin D resulting in secondary hyperparathyroidism. AEDs also inhibit the cellular response to PTH resulting in increasing bone remodeling" [18]. The aim of this work was to assess the bone mineral density (BMD) in children with epilepsy getting anti-epileptic drugs for prolonged periods of time.

2. METHODOLOGY

This study was conducted in the Saleh Child Development and Disability Management Center (SCDDMC), of Institute of Child and Mother Health (ICMH) Matuail, Dhaka. A total of 31 childrens age ranged 5-15 years diagnosed as epilepsy on the basis of both clinical examination and investigation (EEG) receiving antiepileptic drugs (AEDS) for at least two years were recruited in this study. All the relevant particulars were collected in a questionnaire data sheet. Clinical examination including general and complete neurological examination and investigations were done as per standard procedure. Using bone Densitometer (GY lunar-DPX-Central DXA scan, USA), the children's lumbar spines (LV1–LV4) were examined. Using these normative data for study children as a reference for distribution, age and gender specific Z-score for all subjects were computed.

2.1 Inclusion Criteria

- Children were diagnosed as epilepsy on the basis of both clinical examination and investigation (EEG) receiving antiepileptic drugs (AEDS) for at least two years.
- Age 5-15 years
- Both sex

2.2 Exclusion Criteria

Children with epilepsy and other medical disorder, which are likely to affect bone metabolism (e.g., endocrine, hepatic, renal, hematological, rheumatologic, and gastrointestinal diseases)**.** Those who were getting vitamin and calcium supplementation.

All data were presented in a suitable table or graph according to their affinity. A description of each table and the graph was given to understand them clearly. All statistical analysis was performed using the statistical package for social science (SPSS) program, and Windows. Continuous parameters were expressed as mean±SD and categorical parameters as frequency and percentage. Comparisons between groups (continuous parameters) were made by Student's t-test. Categorical parameters compared by Chi-Square test. The significance of the results as determined by a 95.0% confidence interval and a value of $P<0.05$ was considered to be statistically significant.

3. RESULTS

A total of 31 children's age ranged 5-15 years diagnosed as epilepsy on the basis of both clinical examination and investigation (EEG) receiving antiepileptic drugs (AEDS) for at least two years were recruited for this study. Table 1 showed the socio demographic characteristics of study children. It was observed that almost two third (61.3%) children age group were in 5 to 10 years and 12(38.7%) were 10 to 15 years. Almost three fourth (74.2%) children were male and 8(25.8%) were female. Almost two third (61.3%) children come from urban area and 12(38.7%) from rural area. Almost half (48.4%) patient's father completed primary level education. More than half (58.1%) patient's mother completed secondary level education.

More than one third (38.7%) patient's father occupation were service holder. All (100.0%) mother occupation were house wife. More than one fourth (25.8%) children had consanguinity. Seven (22.6%) children had family history of epilepsy. Table 2 showed the perinatal factors related with the study children. It was observed that almost three fourth (71.0%) patients had NVD and 9(29.0%) had LUCS. Almost two third (64.5%) children had history of perinatal asphyxia. Table 3 showed the type of seizure among study children. It was observed that more than two third (67.7%) children had generalized seizure and 10(32.3%) had focal seizure among generalized seizure 12(57.1%) had generalized tonic clinic, 5(23.8%) had tonic, 3(14.3%) had myoclonic and 1(4.8%) had clonic seizure. Table 4 shows The mean duration of phenobarbitone (PB) was 5.85±2.54 yrs with ranged from 2 to 10 yrs. The mean duration of valproic acid (VPA) was 4.77±2.35 yrs with ranged from 2 to 8 yrs. The mean duration of carbamazipine (CBZ) was 4.67±0.58 yrs with ranged from 4 to 5 yrs. The mean duration of nitrazipum (NTZ) was 4.27±2.05 yrs with ranged from 2 to 7 yrs. The mean duration of combination therapy was 4.24±2.02 yrs with ranged from 2 to 7 yrs. Table 5 showed the type of Anti-epileptic drugs used in study children. It was observed that almost two third (61.3%) children had polytherapy and 12(38.7%) had mono therapy. Table 6 shows the mean serum calcium was 9.22±0.78 mg/dl with ranged from 7.8 to 11.5 mg/dl. The mean BMD score of spine was 0.66±0.14. The mean BMD neck of left femur was 0.66±0.15. The mean BMD Neck of right femur 0.66±0.15. More than two third (67.7%) children had low (<-1SD) BMD Z score.

Table 1. Socio demographic characteristics of study children (n=31)

Socio demographic characteristics	Number	Percentage
Age group		
5 to 10	19	61.3
10 to 15	12	38.7
Sex		
Male	23	74.2
Female	8	25.8
Residence		
Urban	19	61.3
Rural	12	38.7
Fathers education		
Below primary	5	16.1
Primary	15	48.4
Secondary	9	29
Above secondary	2	6.5
Mothers education		
Below primary	2	6.5
Primary	11	35.5
Secondary	18	58.1
Fathers occupation		
Farmer	6	19.4
Service	12	38.7
Self employment	2	6.5
Business	7	22.6
Day labourer	4	9.7
Mothers occupation		
House wife	31	100
Consanguinity		
Yes	8	25.8
No	23	74.2
Family history of epilepsy		
Yes	7	22.6
No	24	77.4

Table 7 showed the name and combination of drugs used in study children. It was observed that more than one third (35.5%) children got PB alone followed by 5(16.1%) got VPA alone, 4(12.9%) in PB with VPA, 4(12.9%) in PB with VPA with others, 3(9.7%) in VPA with NTZ, 2 (6.5%) in PB with VPA with NTZ and VPA Alone. Table 8 showed association between type of therapy with BMD Z score of study children. It was observed that almost two third (60.0%) children had mono therapy in BMD Z score normal (>-1SD) and 6(28.6%) in BMD Z score low (<-1SD). Almost three fourth (71.4%) children got poly therapy showed low BMD and 4(20.0%) got poly therapy showed normal BMD Z score. The difference was statistically not significant ($p > 0.05$) between type of therapy with BMD Z score.

Table 2. Perinatal factors related with epilepsy (n=31)

Mode of delivery	Number	Percentage
NVD	22	71
LUCS	9	29
Perinatal history		
Perinatal asphyxia	20	64.5
Meningitis	4	12.9
Septicaemia	1	3.2
No complication	6	19.4

Table 3. Type of seizure among study children (n=31)

Type of seizure	Number	Percentage
Generalized	21	67.7
Generalized tonic clonic	12	57.1
Tonic	5	23.8
Clonic	1	4.8
Myoclonic	3	14.3
Focal seizure	10	32.3

Table 4. Duration of AEDs used in study children (n=31)

AEDs	n	Mean ± SD (years)	Range (min,Max) (years)
Phenobarbitone (PB)	26	5.85±2.54	2,10
Valproic acid (VPA)	13	4.77±2.35	2,8
Carbamazipine (CBZ)	3	4.67±0.58	4,5
Nitrazipum (NTZ)	11	4.27±2.05	2,7
Combination	17	4.24±2.02	2,7

Table 5. Type of Anti epileptic drugs used in study children (n=31)

Type of therapy	Number of children	Percentage
Mono therapy	12	38.7
Poly therapy	19	61.3

Table 6. Serum calcium and BMD level of study children (n=31)

Parameters	Mean±SD	Range (min, Max)
S.calcium mg/dl	9.22±0.78	7.8,11.5
BMD Spine	0.66±0.14	0.34,1
BMD Neck left femur	0.66±0.15	0.4,1.1
BMD Neck right femur	0.66±0.15	0.35,1.12
BMD Z Score (category)	Number of children	Percentage
Normal (>-1SD)	10	32.3
Low (<-1SD)	21	67.7

Table 7. Name and combination of drugs used in study children (n=31)

Name of drug	Number of children	Percentage
PB alone	11	35.5
VPA alone	2	6.5
PB with VPA	4	12.9
PB with NTZ	5	16.1
VPA with NTZ	3	9.7
PB with VPA with NTZ	2	6.5
PB with VPA with others	4	12.9

Table 8. Association between type of therapy with BMD Z score of study children (n=31)

Type of therapy	BMD Z score				*p* value
	Normal (>-1SD)(n=10)		Low (<-1SD)(n=21)		
	n	%	n	%	
Mono therapy	6	60	6	28.6	
Polytherapy	4	40	15	71.4	0.093^{ns}

4. DISCUSSION

This study was done among epileptic children to asses BMD who were getting long-term AEDs total 31 children were studied. In this study, regarding the socio-demographic characteristics of study children, it was shown that almost two-thirds (61.3%) of children were in the age group 5 to 10 years followed by 12(38.7%) were 10 to 15 years. Almost three fourth (74.2%) of children were male and 8(25.8%) were female. More than one-fourth (25.8%) of children had consanguinity. Seven (22.6%) children had a family history of epilepsy.Hasaneen et al. (2017) found that out of 70 epileptic children two third were in the age range between 3 and 13 years (mean age 7.7 ± 3.2 years), and almost two-thirds were male. These findings are nearly similar to the current study [19]. “In another study, observed that among 60 epileptic patients, 38 males (63.3%) and 22 females (36.7%) diagnosed as having epilepsy on the basis of both clinical examination and investigation receiving antiepileptic drugs (AEDS) for at least one year” [20]. “The male-to-female ratio for children with epilepsy was 1.3:1. Regarding consanguinity, reported that consanguineous marriage in 53% of parents of epileptic children in Saudi Arabia” [21,22]. “The authors also stated that consanguineous marriage could be related to a high incidence of epilepsy seen in their study population” [23]. In the current study, consanguinity was found in 25.8% which is not similar to the study of [22]. “That study was done in Saudi Arabia where marriage among the same family is more prevalent. However, another study was done in BD to measure the association of consanguinity between parents and the occurrence of adverse health effects in their children they found consanguinity was 33.85% in the case and 12.5% control group. Parental consanguinity was significantly associated with epilepsy, neurometabolic diseases and storage diseases observed that a family history of epilepsy (FHE) had a significant impact on the occurrence of epilepsy among offspring this may underlie the presence of a genetic etiology. They also concluded that temporal epileptic discharges were the best predictor for FHE, which may suggest the presence of familial temporal lobe epilepsy” [24]. “Similarly, reported that a positive family history of epilepsy increased the risk of developing epilepsy 4.75 times in their study” [25]. In the current study, It was observed that almost three fourth (71.0%) patients had NVD and 9(29.0%) were LUCS delivery. Almost two thirds (64.5%) of children had a history of perinatal asphyxia. Perinatal asphyxia causing early brain injury might develop epilepsy in early childhood. Thomas et al. (2011) observed out of 468 normal vaginal delivery and 356 cesarean delivery, 9 (1.9%) and 4 (1.1%) developed epilepsy later in the childhood period respectively [26]. There was a significant association between childhood epilepsy and a history of perinatal asphyxia [27]. “They observed that 13(10.1%) out of 129 children developed epilepsy: all had neonatal seizures and brain injury on neonatal MRI. Of the newborns with neonatal seizures, 25% (15.8/1000 person-years) developed epilepsy, with the highest hazard ratios (HR) in the newborns with status epilepticus. Children with severe or near-total brain injury were more likely to develop epilepsy compared with those with only mild or moderate injury. The current study found 64.5% had perinatal cause and

perinatal brain injury associated with epilepsy. In this study, regarding the sunlight exposure and food habit of study children, it was observed that more than two third (67.7%) of children had adequate sun exposure and 10(32.3%) had inadequate. More than three fourth (77.4%) of children had calcium and vitamin D-rich food intake most of the day per month diet and 7(22.6%) in calcium and vit D-rich food intake few days per month. In a study conducted in Malaysia, Fong et al. (2016) also observed that vitamin D deficiency is prevalent among pediatric epilepsy patients and one of the risk factors of in those children was lower daily sun exposure behavior which correlates well with our study" [28]. Moreover, they reported that a significantly high proportion of Malaysian children with epilepsy did not achieve the recommended vitamin D and calcium intake, with only 5.7% and 11.9% meeting the recommended vitamin D and calcium intakes respectively.In this study, it was observed that more than two-thirds (67.7%) children had generalized seizures and 10(32.3%) had focal seizure. Among the generalized seizures, 12(57.1%) generalized tonic clonic, 5(23.8%) tonic, 3(14.3%) myoclonic and 1(4.8%) clonic. Osman et al. (2017) reported that among the epileptic children, 35 (58.3%) were with generalized tonic clonic seizures, 11(18.3%) had partial, 10(16.7%) had partial secondary generalization, 4(6.7%) had absence seizures which is almost comparable to our study [20]. In the current study, it was observed that almost three fourth (58.1%) of children had behavioral problems followed by 18(58.1%) children had developmental delay, 9(29.0%) had CP with developmental delay. In a study, authors stated that epilepsy in children is associated with variable comorbidities although the frequency of such comorbidities is often difficult to determine [29]. However, Kariuki et al. (2012) observed that there is a notable association between behavioral problem, mental retardation and developmental delay in children diagnosed as epilepsy [30]. They also reported that active epilepsy, cognitive impairment, and focal seizures were the most significant independent covariates of behavioral problems. Current study showed almost three fourth (74.1%) of children had global developmental delay followed by 5(18.5%) had speech delay, 1(3.7%) had motor delay and cognitive delay. In accordance with our study, authors reported that Global developmental delay (GDD) and intellectual disability (ID) affect up to 3% of the pediatric population [31,32]. The diagnosis of GDD is limited to children younger than 5 years old, but these children often evolve to meet diagnostic criteria for ID and probably represent the same population. In this study, regarding the age at diagnosis of epilepsy among study children, it was observed that the majority (96.8%) child belonged to age ≤10 years and 1(3.2%) in >10 years. The mean age was 2.58±2.63 years with a range from 1 to 12 years. The incidence rate of epilepsy was 144 per 100 000 person-years in the first year of life and 58 per 100 000 for ages 1 to 10 years. The cumulative incidence of epilepsy was 0.66% at age 10 years, with 0.62% having active epilepsy. They concluded that approximately 1 out of 150 children is diagnosed with epilepsy during the first 10 years of life, with the highest incidence rate observed during infancy which is consistent with our study. In this study, epileptic children were treated with antiepileptic drugs. It was observed that almost two thirds (61.3%)of children got polytherapy and 12(38.7%) monotherapyrapy.In a comparable study, that forty-five of the 139 children (32.4 %) were on multiple AED; 42 were on dual therapy while three were on triple therapy [33]. The most common drug combination was sodium valproate and carbamazepine, 34/45 (75.5 %) followed by carbamazepine and phenobarbitone, 6/45 (13.4 %) and sodium valproate and phenobarbitone, 2/45 (4.5 %). Of the 94/139 participants on monotherapy, 54/139 (38.8 %) were on carbamazepine only, 37/139 (26.6 %) were on sodium valproate only, two were on phenobarbitone and one was on phenytoin only. Regarding seizure control; thirteen children on multi AED therapy, 13/45 (28.9 %) had good seizure control compared to 61/94 (64.9 %) patients on monotherapy. In this study, the mean serum calcium was 9.22±0.78 mg/dl with a range from 7.8 to 11.5 mg/dl. The mean BMD spine was 0.66±0.14 with ranged from 0.3 to 4.1. The mean BMD neck of left femur was 0.66±0.15 with ranged from 0.4 to 1.1. The mean BMD Neck of right femur 0.66±0.15 with ranged from 0.35 to 1.12. More than two third (67.7%) children had low (<-1SD) BMD Z score. Reduction in bone mineral density at lumbar spine (standardized mean difference (SMD)=−0.30, 95% confidence interval (CI) 0.61, −0.05 [34]. The mean BMD neck left femur was 0.66±0.15 with ranged from 0.4 to 1.1. The mean BMD Neck right femur 0.66±0.15 with range from 0.35 to 1.12. The mean total serum calcium levels were 9.48 (SD 0.83) mg/dL which is comparable to our study [35]. There was a statistically significant moderate correlation between the duration of carbamazepine therapy and total calcium level (r

= 0.36; P=0.001). The cut-off point for duration of therapy was 23 months. There was no significant correlation between total calcium level and mean daily carbamazepine dose, or between total calcium level and duration and dose of valproic acid therapy. This study observed that common AEDs were used in study children. More than one third (35.5%) children got PB alone followed by 5(16.1%) got VPA alone, 4(12.9%) got PB with VPA, 4(12.9%) got PB with VPA with others, 3(9.7%) got VPA with NTZ, 2 (6.5%) got PB with VPA with NTZ and 2 (6.5%) got VPA alone. Epilepsy is the tendency to have recurrent, unprovoked seizuresstated that although 70% of epileptic seizures can be controlled with monotherapy (treatment by single antiepileptic drug), a combination of two or more anti-epileptic drugs (AEDs) may be required to improve efficacy (seizure control) and tolerability [36]. Polytherapy (treatment with two or more AEDs) can affect efficacies and side effects in additive, supra-additive (synergistic) or infra-additive fashion. In this study, regarding the association between types of therapy with BMD Z score of study children, it was observed that almost two third (60.0%) children had mono therapy in BMD Z score normal (>-1SD) and 6(28.6%) had BMD Z score low (<-1SD). Almost three fourth (71.4%) children got poly therapy showed low BMD and 4(20.0%) got poly therapy showed normal BMD Z score. Though the difference was statistically not significant (p > 0.05) between types of therapy with BMD Z score. “Epileptic patients had lower BMD, Z- score, and AM compared with controls (P value < .001)” [20]. “Epileptic patients with LBMD had significant decrease in Z score, BMD and AM (P < .001) compared with epileptic patients with normal bone state. Many studies have shown a significant reduction in bone mineral density (BMD in patients treated with enzyme-inducing antiepileptics” [7]. “Increasing duration of anti-epileptic drug treatment may increase risk of osteopenia and fractures” [11].

5. CONCLUSION AND RECOMMENDATIONS

In summary, among the all epileptic children in this study more than two third showed low BMD.Epileptic children received multiple AEDs (Polytherapy), nearly three fourth showed low bone mineral density. The children those who got longer duration of PB showed low BMD. Therefore, it is necessary to be cautious about the conclusions. Scientifically designed, randomized controlled trials and blind methods should be carried out in future clinical research, and multi-centre large sample studies should be conducted if necessary.

6. LIMITATIONS OF THE STUDY

Every hospital-based study has some limitations and the present study undertaken is no exception to this fact. The limitations of the present study are mentioned. Therefore, the results of the present study may not be representative of the whole of the country or the world at large. The number of patients included in the present study was less in comparison to other studies. Vitamin D status was not evaluated as it is costly.

Because the trial was short, it was difficult to remark on complications and mortality.

CONSENT

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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