INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com
ISSN 2230 – 8407

Research Article

IMPACT OF PHARMACEUTICAL CARE ON BONE HEALTH IN EPILEPTIC WOMEN TAKING ANTIEPILEPTIC DRUGS: AN INTERVENTIONAL TRIAL

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Article Received on: 22/06/18 Approved for publication: 29/07/18

DOI: 10.7897/2230-8407.097144

ABSTRACT

Antiepileptic drugs (AEDs) have adverse effects on bone mineral density (BMD) and an inverse relationship exists between bone health and the use of anti-epileptic drugs. The quality of bone is affected by the duration and the type of anti-epileptics used. Adults, particularly women are at more risk. The aim of the trial was to determine the impact of pharmaceutical care on bone mineral density of epileptic women taking AEDs for at least two years. Participants (n = 29) were randomly assigned to either control group or intervention group. The control group patients received usual physician care while the intervention group received interventions from a clinical pharmacist like educational intervention and pharmacotherapy intervention in the form of supplements. Primary outcome measures were femoral neck and lumbar spine BMD, which is expressed as T-score. BMD was determined by dual-energy X-ray absorptiometry (DEXA) in 30 epileptic women taking AEDs for more than two years. Outcomes were assessed at baseline and 12 months in both groups. The mean (±SD) changes in BMD in the intervention and control groups were: femoral neck +0.52±4.81 and -0.71±5.03 respectively ($p<0.01$) and spine +2.15±4.01 and +1.22±4.23 respectively ($p<0.01$). The difference between the interventional and control groups was significant at femoral neck and lumbar spine regions. We found that supplementation with calcium and vitamin D moderately reduced bone loss measured in femoral neck and lumbar spine regions over a one-year period through pharmacist-led intervention. Overall, the current study underscores the importance of pharmacist's intervention on bone health in epileptic women.

Key words: antiepileptics, epileptic women, BMD, T- score

INTRODUCTION

Epilepsy is an episodic neurological disorder that has afflicted humankind throughout recorded history. Epilepsy is a disorder that is best viewed as a symptom of disturbed electrical activity in the brain, which may be caused by a wide variety of etiologies.The ultimate goal of treatment for epilepsy is complete elimination of seizures and no side effects with an optimal quality of life, but persons with epilepsy taking some antiepileptic drugs (AEDs) are at risk for bone disease. In epileptic population, fracture risk is increased two to six times that of general population and also about 40% of fractures were directly related to seizures[1]. In adults, peak bone mineral density (BMD) is attained between the ages of 20 and 30 years. After age 30, there is a gradual decline in BMD. In women, this is most pronounced in the years following the onset of menopause. AEDs may superimpose an additional effect on bone health; therefore, adults, particularly women taking AEDs are at even greater risk for bone diseases such as osteopenia/osteoporosis, and for fracture[2]. The incidence of hip fracture is >700 per 100,000 person-years among women and >300 per 100,000 person-years among men with wide variations within specific population groups and with exponential increases in risk as age increase[3]. If the incidence rates remain stable, with the aging of the global population, the number of hip fractures worldwide is projected to rise from 1.7 million in 1990 to 6.3 million in 2050[4]. Vitamin D metabolism and bone turn over are the two major reasons for decreasing BMD during AED therapy. AED-induced bone loss has been focused on those drugs that induce the hepatic cytochrome P450 enzyme system, thereby increasing the metabolism of vitamin D. Mechanisms may include direct effects of AEDs on bone cells, resistance to parathyroid hormone, inhibition of calcitonin secretion, and impaired calcium absorption, besides hepatic enzyme induction[5]. Dual energy X-ray absorptiometry (DEXA) is a widely used technique to assess the bone mineral density at different skeletal sites and thus differentiate individuals with low bone mass who are at risk of osteoporosis and fractures[6]. Practically, pharmacists may play a role in narrowing gaps in osteoporosis diagnosis and treatment adherence. First, pharmacists may help identify high-risk patients. Second, pharmacists can provide counseling and educate patients on medication use, fall prevention, and the importance of calcium, vitamin D, exercise, and adherence to therapy. A recent review identified that non-drug interventions by healthcare professionals improved quality of life, treatment adherence, and calcium intake among community-dwelling postmenopausal women with osteoporosis[7]. Hence, this study aims to establish the relationship between the bone health and AED use the impact of pharmacist's intervention as well in improving the bone health, particularly in women epileptic patients taking AEDs.

MATERIALS AND METHODS

Study design

This is a prospective, randomized controlled, interventional trial where the study subjects were randomly assigned to either control group or interventional group. The study has been registered in Clinical Trial Registry – India (CTRI) and the registration number is CTRI/2015/08/006103.Ethical clearance was obtained from

Institutional Ethics Committee, KG Hospital and Postgraduate Research Institute, Coimbatore, India.

Participants

Premenopausal women epileptic patients (n = 43) were taken into the study. Subjects were enrolled at KG Hospital and Postgraduate Research Institute, Coimbatore, India between January 2014 and September 2014. Inclusion criteria were women living in Coimbatore or its environs; age equal to or greater than 20 years; use of AEDs for at least two years; regular menses; and willingness to participate in the study. Exclusion criteria were mental retardation; immobilization; presence of conditions known to affect bone metabolism such as hepatic, hematological, rheumatologic or renal disorders, overt bone deformities, hyperparathyroidism, osteogenesis imperfecta, hyperthyroidism, gastrointestinal disorders (e.g., malabsorption), hypogonadism, medications known to affect bone turnover like bisphosphonates, glucocorticoids, thiazides, anticoagulants, GnRH analogues or steroids, and patients who are on calcium or vitamin D supplementation. Of the 43 patients enrolled, 14 (30%) discontinued participation. Reasons for discontinuation included lost to follow up (n=8); pregnancy (n=1); time constraints (n=4); and moved from the city (n=1). This report includes 29 subjects with both baseline and one-year follow up measures. All the participants were receiving single AED (Phenytoin, carbamazepine, lamotrigine, or valproate) at least two years before enrollment.

Procedure

The study was approved by the institutional ethics committee of KG Hospital and Postgraduate Research Institute. The clinical pharmacist explained the detailed purpose of study and benefits in local language to the individual patient and caretaker. Patient consent was obtained without any form of force or compulsion. The patients were randomized into control and intervention groups through a simple randomization method. All participants provided information about time of diagnosis and treatment of epilepsy, frequency of seizures, type and dose of AED and previous fractures. Detailed clinical histories were taken including menarchal age and reproductive history. Height and weight were measured and body mass index was calculated. These evaluations were completed at baseline and after one year of observation. Average daily dietary calcium intake was estimated from reported intake of dairy products and categorized into three tertiles: < 400 mg, 400-800 mg, and >800mg. Because caffeine content of brewed beverages varies widely, the caffeine content of 8 ounces of coffee, tea, and cola drinks was set at 100 mg, 47 mg, and 40 mg, Respectively[8]. Average daily caffeine intake was categorized as low (<200 mg), medium 200-400 mg and high (>400 mg). Physical activity was considered moderate when it was performed on a regular basis at least three hours per week.

At the start of study, BMD test was taken in both groups and t-score was analyzed. According to the baseline BMD T-score, the clinical pharmacist categorized the patients as low, medium, or high risk. Each subject had BMD measured at entry and one year on the same densitometer (Hologic 1000 and 4500 densitometers; Hologic, Waltham, MA). If the values were less than -1.0, then the intervention group patients were given calcium in the form of 500 mg of elemental calcium in the form of calcium citrate malate and 700 IU of cholecalciferol[9]. In addition to this, intervention group patients were given counseling and awareness about the importance of maintaining bone health. If they were at risk or osteopenic, they were told about dietary and lifestyle approaches to be adopted which includes ample amount of milk, nuts especially almonds, dates and exposure to the sunlight especially in the morning time before 9'o'clock. It was followed up for a period of one year. The patients in the control group received usual care from the neurology outpatient department of the hospital. After one year, when the patients came for follow-up, second BMD was taken in patients in both groups. It was then tabulated and analyzed.

Analysis

The major statistical software used for analysis was SPSS statistics version 17.0 and statistical approach to find out t-value and P-value was student t-test or paired sample t-test. Then correlation between different variables in the demographic details of the patient and t-score had been evaluated. This was to focus the various factors beyond the reduction of bone health in epileptic females on long term AED therapy.

RESULTS

Characteristics of study population:

The mean age of patients was 33.69 years in control group and 33.72 in intervention group and mean BMI was 24.7 in control group and 25.2 in intervention group. The age of menarche was more or less same in both groups viz., around 13 to 14 years of age. Number of pregnancies was less than three in both control and intervention groups. About 60% of the study population was taking 400-800 mg of calcium through dietary foods and around 70% were taking medium level of caffeine in the form of beverages.

The age of onset of epilepsy was around 18 years and the duration of epilepsy was around 13 years in both control and intervention groups. The number of anti-epileptic medications was 2 and the mean seizures per month were 2 in both groups. Majority of the study population was having partial secondary generalization type of seizures (Table 1).

Bone Mineral Density of the patients which was measured using DEXA was analyzed with the help of T-score. The range of T-score values are then categorized into four groups (Table 2).

T-score Report

There is a positive impact of pharmaceutical care in the interventional group as there is improvement in T-score after one year of follow-up (Table 3). Osteoporotic frequency found to be greatly reduced from 7% to 0% in spine region and 21% to 14% in hip region in interventional group compared to marginal change in control group. 21% of interventional subjects had been recovered from the poor bone mineral density to normal within one year of follow-up without compromising the efficacy of anti-epileptic therapy. Only 7% of the control group had recovered normal bone health. This means that that there is a positive impact of pharmaceutical care in improving the health-related quality of life, which was compromised due to long term anti-epileptic drug therapy.

There is a frequency of shifts between three tertiles in control and interventional group to ease the picturization of pharmaceutical care in interventional group. Mean deviation of T-score for control group was found to be -0.80±2.91 (spine) and -0.47±0.97 (femoral neck) at baseline and -0.72±2.13 (spine) and -0.42±0.95 (femoral neck) after one year i.e., there is only small difference in T-score (Table 4).
Mean deviation of T-score for interventional group at baseline and after one year shows a significant T-score difference of

0.44±1.65 at spine and 0.87±0.07 at hip, which is because of pharmacists' intervention and supplementation.

At 0.01% level of significance (Confidence Interval-99%), P value was below 0.01. Thus, the study was significant for two-tailed test. It implicates that there was a positive impact in the bone health of epileptic females by pharmacist intervention.

Table 1: Baseline characteristics of study subjects

Sl No.	Variables	Control group (n=15)	Intervention group (n=14)
	Patient Demographics		
1.	Age (mean ± SD)	33.69 ± 9.08	33.72 ± 8.01
2.	Mean height (mean ± SD)	154.4 ± 4.8	156.2 ± 4.5
3.	Mean weight (mean ± SD)	58.3 ± 8.1	59.2 ± 7.6
4.	Mean BMI (mean ± SD)	24.7 ± 2.9	25.2 ± 3.1
5.	Age at Menarche (mean ± SD)	13.7 ± 1.1	13.5 ± 1.2
6.	No. of Pregnancies (mean ± SD)	2.2 ± 0.7	2.7 ±1.1
	Diet		
	Daily calcium:		
7.	< 400 mg	4 (26%)	3 (21%)
8.	400-800 mg	9 (60%)	10 (71%)
9.	>800mg	2 (13%)	1 (7%)
	Daily caffeine intake:		
10.	Low (<200 mg)	3 (20%)	2 (14%)
11.	medium 200-400 mg	10 (67%)	11 (78%)
12.	high (>400 mg)	2 (13%)	1 (7%)
	Epilepsy characters		
13.	Age of onset of epilepsy (mean ± SD)	18.2 ± 12.8	18.6 ± 13.1
14.	Duration of epilepsy in years (mean ± SD)	13 ± 7.1	13.2 ± 7.3
15.	Number of seizures per month (median)	3	3
16.	Number of AED (median)	2	2
	Type of seizures		
17.	Partial without generalization	5(33.3%)	4 (28.5%)
18.	Primarily generalized	1(6.6%)	2 (14.2%)
19	Partial with secondary generalization	9(60.0%)	8 (57.1%)
	Etiology		
20.	Symptomatic	10(66.6%)	9 (64.2%)
21.	Cryptogenic	4(26.6%)	4 (28.5%)
22.	Idiopathic	1(6.0%)	1 (7.1%)

Table 2: Categories of epileptic patients according to the T-score values

T-score values	Category
All positive values (>0)	Normal
0.0 to -0.9	Risk
-1.0 to -2.4	Osteopenic
Less than -2.5	Osteoporotic

Table 3: Bone mineral density at baseline and after one year of anti-epileptic treatment

Categories of T-score	Baseline		After one year	
	C (%) (n=14)	I (%) (n=15)	C (%) (n=14)	I (%) (n=15)
SPINE				
Normal	0(0%)	0 (0%)	1(7%)	3 (21%)
Risk	8 (57%)	8 (57%)	7 (50%)	9 (64%)
Osteopenic	5(35%)	6 (43%)	5 (35%)	3 (21%)
Osteoporotic	1 (7%)	1 (7%)	1 (7%)	0 (0%)
HIP				
Normal	0 (0%)	0 (0%)	1 (7%)	3 (21%)
Risk	7 (50%)	7 (50%)	8 (57%)	8 (57%)
Osteopenic	4 (28%)	5 (35%)	3 (21%)	2 (14%)
Osteoporotic	3 (21%)	3 (21%)	2 (14%)	2 (14%)

C=Control group; I= Interventional group

Table 4: Frequency of T-score shifts between three tertiles in control and interventional group

Site of T-score	Baseline		After one year		MD		P Value
	C (n=14)	I (n=15)	C (n=14)	I (n=15)	C	I	
Spine	-0.80±2.91	-0.90±3.08	-0.72±2.13	-0.46±1.43	0.08±0.78	0.44±1.65	<0.001
Femoral Neck	-0.47±0.97	-0.51±0.96	-0.42±0.95	0.36±0.89	0.05±0.02	0.87±0.07	<0.001

Data expressed as Mean ±SD; C= Control group; I= Interventional group; MD= Mean Deviation

DISCUSSION

In this study the DEXA results shows that there is a significant improvement in bone health in interventional group compared to control group. The change in the T-score can be easily demonstrated from the mean difference values of T-score from table-4. The rate of increase of T-score in interventional group is much greater compared to control group. There is an increase of 0.44 score in spine and 0.87 score in femoral neck in interventional group, while there is only 0.08 increase in spine and 0.05 increase in femoral neck in control group.

From this study, we can prove that vitamin D and calcium supplements along with pharmaceutical care intervention can improve bone health in epileptic patients who are under anti-epileptic drug treatment along with dietary consideration and exposure to sunlight.

There is no correlation between age and reduction in BMD; although a negative correlation was found between duration of therapy and BMD. Therefore, duration of therapy was found to be significant negative determinants of BMD[8]. Earlier studies included institutionalized persons and did not control for confounding variables such as inadequate diet and sunlight exposure. More recent studies have evaluated ambulatory patients and have reported findings similar to ours. A study of non-institutionalized persons revealed a fourfold increased risk of femoral neck fractures when compared with age and sex-matched controls. Another study that included 71 adults and children found AED use and duration of AED therapy to be significantly correlated with low BMD[9].

CONCLUSION

Supplementation with calcium and vitamin D moderately reduced bone loss measured in femoral neck and lumbar spine regions over a one-year period through pharmacist-led intervention. The results obtained from the study suggest that pharmacists are in a better position to give counseling about the side effects of AEDs and improve the bone health by proper pharmacotherapeutic interventions. Overall, the current study underscores the importance of pharmacist's intervention on bone health in epileptic women.

ACKNOWLEDGEMENT

We gratefully acknowledge KG Hospital and Postgraduate Research Institute, Coimbatore, India for providing all technical support.

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Cite this article as:

Sabna M and Anphil Thomas. Impact of pharmaceutical care on bone health in epileptic women taking antiepileptic drugs: An interventional trial. Int. Res. J. Pharm. 2018;9(7):173-176 http://dx.doi.org/10.7897/2230-8407.097144

Source of support: Nil, Conflict of interest: None Declared