EFFICACY AND SAFETY OF THE COMBINATION OF ALENDRONATE AND CHOLECALCIFEROL IN THE TREATMENT OF OSTEOPOROSIS IN CHRONIC HEMODIALYTIC PATIENTS

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Abstract
Background: Osteoporosis increases morbidity and mortality in patients on chronic hemodialysis. There are some preliminary studies that demonstrated the safety and the efficacy of bisphosphonate group, especially alendronate in treating osteoporosis in patients with chronic kidney failure. **Objectives:** To determine the efficacy and the safety of alendronate combined with cholecalciferol in osteoporosis treatment in patients on chronic hemodialysis. **Methods**: We conducted a non-controlled interventional trial. All chronically hemodialytic patients diagnosed with osteoporosis at one or more regions of interest: neck, trochanter, intertrochanter, Ward triangle and total neck were given 70 mg alendronate combined with 2800 IU cholecalciferol once a week. They were indicated bone density measure by dual energy absorptiometry 3 times: at the beginning, 3 months and 6 months after treatment initiation. Primary outcome was improvement in bone density and prevalence of osteoporosis. **Results:** We included 32 patients in this trial. The prevalence of osteoporosis at the neck, trochanter, intertrochanter, Ward triangle and total neck were 93.8%; 31.3%; 56.3%; 81.3% and 68.8% respectively. The bone density trended to improve after 3 months and 6 months, although not significantly. The prevalence of osteoporosis showed a decrease from 100% to 90.6% after 6 months, but this change was not statistically significant. Duodenal gastric symptoms appeared in 4 patients, but all of them were well controlled with proton pump inhibitors. **Conclusion**: Alendronate combined with cholecalciferol showed efficacy and safety in the treatment of osteoporosis in hemodialytic patients. The preliminary results showed a non-significant improvement of the bone density and of the osteoporosis prevalence. Perhaps it requires another longer and larger trial to visualize these improvements.
Key words: *osteoporosis, DEXA, chronic renal failure, chronic hemodialysis*

1. INTRODUCTION

One factor reducing the quality of life and increase mortality in hemodialytic patients is osteoporosis and its related fractures [14]. The osteoporosis treatment aimed to the reduction of the fracture was mostly studied in postmenopausal women, with bisphosphonate, estrogen receptor modulator, parathyroid hormone and some other groups. The evidences of their benefices are strongly proved [3]. However, the osteoporosis treatment in hemodialytic patients is still in discussion. Ones believe that their bone turnover is already low, so the drugs suppressing the osteoclasts will have no benefits [12]. Although, some articles showed that the bisphosphonate group had some role in the osteoporosis treatment and in the fracture risk reduction in these patients [5],[15].

So we conducted this study to determine the safety and the efficacy of the combination of alendronate and cholecalciferol in the treatment of osteoporosis in hemodialytic patients.

2. METHODS

Design: this is an interventional study.

Inclusion criteria

We included in this study all patients on chronic hemodialysis with the diagnosis of osteoporosis (WHO criteria [8]) at the Department of Hemodialysis at Cho Ray Hospital from December 2013 to the end of August 2014.

Exclusion criteria

- The patient cannot keep the sitting up position for at least 30 minutes

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- Esophageal cancer, Barrett esophagus, esophageal ulcer
- Active gastritis, peptic ulcer, gastrointestinal reflux disease
- Allergy to alendronate or to cholecalciferol
- The patient do not agree to join the study

Outcome: the improvement of bone mineral density and the prevalence of osteoporosis

Study protocol

All patients were treated with the combined tablet containing 70 mg alendronate and 2800 IU of cholecalciferol (Fosamax plus ®, Merck Sharp & Dohme, registration number VN-17522-13). The patients were assessed the bone mineral density (BMD) at five regions of interest: femoral neck, trochanter, intertrochanter, Ward's triangle and total hip by the machine Hologic Explorer QDR4500. The assessments were indicated three times: at the beginning, 3 months and 6 months after the treatment.

Some definitions

The diagnosis of osteoporosis was based on World Health Organization criteria [4]

Table 1. Criteria of diagnosis of osteoporosis

Diagnosis	Criteria
Normal	T-score ≥ -1
Osteopenia	-2.5 < T-score < -1
Osteoporosis	T-score ≤ -2.5
Severe osteoporosis	Osteoporosis + recent history of fracture

End-stage renal disease is defined as chronic kidney disease stage 5 (KIDIGO 2012) [11]

Table 2. Stages of chronic kidney disease

Stage	Description	Glomerular filtration rate (GFR) (mL/ minutes/1,73m^2)
1	Normal or increased GFR	≥ 90
2	Mildly decreased GFR	60 – 89
3a	Mildly to moderately decreased GFR	45 – 59
3b	Moderately to severely decreased GFR	30 – 44
4	Severely decreased GFR	15 – 29
5	Renal failure	< 15

Data analysis

The data was inputted by the software Excel 2010, analyzed by IBM SPSS version 21.0.

The quantitative variables were described as mean ± standard deviation (SD), the qualitative variables were described as percentage number.

We used these statistical tests in our study:

Paired T-test to compare the BMD, T-score before and after the treatment

T-test to compare the BMD of 2 groups with and without risk factors of osteoporosis

Z-test to compare the prevalence of osteoporosis before and after the treatment

The difference is statistically significant if p-value is inferior to 0.05

3. RESULTS

We included 32 patients in this study, of them 71.9% female. All of them were given the combination tablet of 70 mg alendronate and 2800 IU vitamin D once a week.

3.1. General characteristics of the studied population

The general characteristics of the population were described in this following table.

Table 3. Characteristics of the studied population

	N	Min	Max	Mean	SD
Age (year)	32	29	89	59.69	16.27
Hemodialysis duration (month)	32	27	161	68.56	40.63
Hemoglobinemia (g/L)	32	65.00	149.00	102.81	17.09
Proteinemia (g/dL)	28	5.10	8.70	7.10	0.72
Albuminemia (g/dL)	29	2.80	4.80	4.13	0.41
Ferritinemia (ng/mL)	31	99.80	2519.00	831.35	600.00
Ironemia (µmol/L)	31	0.50	32.40	11.20	7.00
Transferrinemia (mg/dL)	31	76.30	310.30	159.25	50.92
Calcemia (mmol/L)	32	1.80	2.80	2.25	0.27
Phosphoremia (mg/L)	31	12.10	95.20	48.23	17.87
Serum PTH (pg/mL)	29	48.80	879.00	272.88	233.00

3.2. Characteristics of bone mineral density

The patients were assessed the bone mineral density (BMD) at five regions of interest: femoral neck, trochanter, intertrochanter, Ward's triangle and total hip by the machine Hologic Explorer QDR4500. The assessments were indicated three times: at the beginning (T0), 3 months (T1) and 6 months (T2) after the treatment. The results were described in these following tables.

Table 4. Bone mineral density at different regions of interest

BMD (g/cm^2)	Min	Max	Mean	SD
Neck	0.394	0.625	0.510	0.065
Trochanter	0.221	0.722	0.488	0.091
Intertrochanter	0.368	1.008	0.690	0.158
Ward's triangle	0.192	0.520	0.367	0.082
Total hip	0.380	0.845	0.610	0.119

Table 5. T-score at different regions of interest

T-score	Min	Max	Mean	SD
Neck	-4.1	-2.0	-3.1	0.6
Trochanter	-4.8	-0.4	-2.2	0.8
Intertrochanter	-4.7	-1.0	-2.7	0.9
Ward's triangle	-4.5	-1.8	-3.0	0.7
Total hip	-4.6	-1.2	-2.8	0.9

3.3. Changes of bone mineral densities during the follow-up

We noticed an increase in bone mineral densities at all regions of interest at T2, although the differences were not statistically significant (Table 6 and Table 7). The difference is most visual at the site Ward's triangle after 6 months at treatment (p=0.05, Table 7).

Table 6. Changes of bone mineral densities at T0 and T1

BMD (g/cm^2)	T0		T1		Δ_1^* ± SD	P
	Mean	SD	Mean	SD		
Neck	0.510	0.065	0.513	0.106	0.002 ± 0.094	0.90
Trochanter	0.488	0.091	0.487	0.108	-0.002 ± 0.056	0.88
Intertrochanter	0.690	0.158	0.714	0.150	0.024 ± 0.108	0.23
Ward's triangle	0.367	0.082	0.380	0.113	0.013 ± 0.095	0.44
Total hip	0.610	0.119	0.614	0.127	0.004 ± 0.083	0.80

*: Δ_1 = BMD at T1 – BMD at T0

Table 7. Changes of bone mineral densities at T0 and T2

BMD (g/cm^2)	T0		T2		Δ_2^* ± SD	P
	Mean	SD	Mean	SD		
Neck	0.510	0.065	0.516	0.087	0.006 ± 0.074	0.66
Trochanter	0.488	0.091	0.490	0.090	0.002 ± 0.064	0.89
Intertrochanter	0.690	0.158	0.697	0.165	0.006 ± 0.108	0.74
Ward's triangle	0.367	0.082	0.399	0.115	0.032 ± 0.091	0.05
Total hip	0.610	0.119	0.620	0.127	0.010 ± 0.080	0.47

*: Δ_2 = BMD at T2 – BMD at T0

Similarly, there were some improvements in osteoporosis prevalence after the treatment, though not significantly.

Table 8. Comparison of osteoporosis rate at T0 and T1

Prevalence of osteoporosis	T0		T1		P
	N	%	N	%	
Neck	30	93.8%	25	78.1%	0.15
Trochanter	10	31.3%	8	25.0%	0.58
Intertrochanter	18	56.3%	18	56.3%	1.00
Ward's triangle	26	81.3%	27	84.4%	0.74
Total hip	22	68.8%	20	62.5%	0.60
All regions	32	100.0%	30	93.8%	0.49

Table 9. Comparison of osteoporosis rate at T0 and T2

Prevalence of osteoporosis	T0		T2		P
	N	%	N	%	
Neck	30	93.8%	25	78.1%	0.15
Trochanter	10	31.3%	11	34.4%	0.79
Intertrochanter	18	56.3%	19	59.4%	0.80
Ward's triangle	26	81.3%	26	81.3%	1.00
Total hip	22	68.8%	17	53.1%	0.20
All regions	32	100.0%	289	90.6%	0.14

3.4. Side effects of the drug

At the beginning of the study, we enrolled 49 osteoporosis patients, but 17 of them having active peptic disease, we then had 32 patients going into the study. After 3 months, there were 4 patients with new onset peptic symptoms, and all of them were well controlled by the proton pump inhibitor group. After 6 months of treatment, there were no patient leaving the study, and we registered no treatment associated severe side effects.

4. DISCUSSION

4.1 Efficacy of alendronate in the treatment of osteoporosis in hemodialytic patients

As the evaluation of the efficacy of the treatment, the results showed that the bone mineral densities trended to increase at all regions of interest, except the neck, after 3 months, and at all regions after 6 months of follow up. The improvement was most visible at the Ward's triangle after 6 months (Table 7). For the prevalence of osteoporosis, there was a small decrease at the neck, trochanter and total hip regions, but a small increase at the Ward region (although not significant) at T1. After 6 months, the prevalence of osteoporosis trended to decrease at the neck and total hip, and to increase at trochanteric and intertrochanteric regions, and rested unchanged at the Ward's triangle (not significant too). After 6 months, the prevalence of osteoporosis changed from 100% to 90.6% (Table 9).

The efficacy of alendronate in the treatment of osteoporosis in the general population had been strongly proved by many trials; one of them was the FIT. This large randomized controlled trial showed that alendronate helped to improve the bone density, as well as reduced the fracture risk in the patients with history of fracture or T-score <-2.5 [6],[7]. Yet, its role in the renal failure patients was still not fully examined. Recently, Jamal reviewed the patients in the FIT, and selected only ones having renal failure. She noticed that alendronate did have the efficacy in the improvement of bone density and in the reduction of fracture risk in this group of patients [10]. Moreover, we found some interventional trials using alendronate in hemodialytic patients. Wetmore (2005) evaluated the short-term effect of alendronate on BMD in 31 patients. The patients were randomized in 2 groups, one group given alendronate and the other placebo. The results showed that the BMD was unchanged after 6 months in the treatment group, but reduced in the placebo group ($p<0.05$). Lumbar bone density slightly increased after 6 months [15]. Iwamoto (2012) resumed his experiences of osteoporosis treatment in 3 years. He observed that there was 26 patients having the glomerular filtration rate inferior to 60 mL/minute/1.73m^2. In those patients, there was a significant increase of lumbar bone density, urine NTX level and blood alkaline phosphatase to the baseline. He also noticed that, even treated, the fracture risk was still higher in the renal failure group than in the normal group [9].

Our results were similar to the other authors, showing a slight increase in bone mineral density, although not statistically significant. It is probably because the follow up duration was not long enough (only 6 months). The FIT results showed that the bone mineral density changed after at least 1 year [6],[7].

For the role of cholecalciferol, the KDOQI guidelines recommend the using of ergocalciferol in the treatment of vitamin D deficiency in chronic kidney disease, or using the active vitamin D metabolites in patients with the serum PTH > 300 g/mL [13]. But all these guidelines do not have strong evidences and are mainly based on expert's opinions. There were some study demonstrating the safety and efficacy of cholecalciferol in the treatment of vitamin D deficiency in chronic kidney disease [8]. That's why we chose to use the combination tablet alendronate and cholecalciferol in this study.

4.2. The safety of alendronate combined with cholecalciferol in the treatment of osteoporosis in hemodialytic patients

As cited, except 4 patients with peptic symptoms, we did not register any other side effects. Our study size is not large, and the follow up course is not very long, so we cannot conclude anything about the safety of the regimen, but at least the results suggested that the drug is relatively safe. Some other studies showed that alendronate had no severe side effect in patients with chronic kidney disease. Jamal reviewing 581 patients with GFR < 45 L/minute treated with alendronate, showed no difference in side effect between the alendronate and the placebo group [10]. Wetmore evaluated the short-term effect of alendronate in hemodialytic patients. The only observed side effect was gastrointestinal reflux observed in 3 patients [15]. Similarly in the patients with GFR < 60 mL/minute, Iwamoto did not register any severe side effect of alendronate [9].

5. CONCLUSION

Alendronate combined with cholecalciferol helped to slightly improve (although not significantly) the bone mineral density in the hemodialytic patients after 6 months of treatment. The prevalence of osteoporosis decreased from 100% to 90.6%. Our results suggested that this drug was safe for the treatment of osteoporosis in this group of patients; the only side effects observed in the study were the peptic symptoms.

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