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Orjinal Makale

Comparison of the Efficacy of Oral and Parenteral Bisphosphonates in Patients with Postmenopausal Osteoporosis: A single-center, retrospective clinical study

Postmenapozal Osteoporozlu Hastalarda Oral ve Parenteral Bifosfonatların etkinliğinin Karşılaştırılması: Tek merkezli retrospektif klinik Çalişma

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ABSTRACT

Aim: The aim of the study is to compare the efficacy of oral and parenteral bisphosphonates used in the treatment of postmenopausal osteoporosis.

Material and Methods: Patients older than 50 years who were diagnosed with postmenopausal OP and treated with oral or parenteral bisphosphonate between 2016 and 2019 were included in the study. The patients were grouped by treatment; 80 patients receiving oral bisphosphonate and 80 patients receiving parenteral bisphosphonate were divided into two groups as group 'O' and group 'P', respectively. The results of the second-year treatment of 160 patients, who were treated regularly and could be followed-up for at least 2 years, were evaluated and compared.

Results: According to the pre-treatment state in both groups; vertebral and femoral bone mineral density (BMD) and T-scores showed significant improvement. The mean improvement in vertebral and femoral T-scores and femoral BMD values was better in group 'P' with a statistically significant difference. In the oral bisphosphonate group, there was a statistically significant difference between the groups in favor of alendronate in the femoral T-score, while, in the parenteral bisphosphonate group, the improvement in the vertebral and femoral T-score was better in the zoledronate subgroup and statistically significant.

Conclusion: This study concluded that oral and parenteral bisphosphonates are effective in the treatment of postmenopausal OP. Nevertheless, parenteral bisphosphonates were found to be more effective in terms of mean improvement in vertebral and femoral T-scores and femoral BMD.

Keywords: DEXA; bisphosphonate; Postmenopausal osteoporosis; zolendronic acid.

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Öz

Amaç: Çalışmamız postmenopozal osteoporoz (OP) tedavisinde kullanılan oral ve parenteral bifosfanatların etkinliklerini karşılaştırmayı amaçlamaktadır.

GereçveYöntemler:2016-2019 yıllarıarasında postmenopozal OP tanısı konularak, oral yada parenteral bifosfonat ile tedavi edilen 50 yaş üstü hastalar çalışmaya dahil edildi.Tedaviye göre oral bifosfonat alan 80 hasta grup 'O' ve parenteral bifosfonatalan 80 hasta grup 'P' olarak iki gruba ayrıldı.Tedavilerini düzenli alan ve en az 2 yıl takibi yapılabilen 160 hastanın tedavinin 2. Yıldaki sonuçları değerlendirilerek karşılaştırıldı.

Bulgular: Her iki grupta tedavi öncesine göre; vertebra ve femur kemikmineralyoğunluğu (BMD) ve T-skorlarında anlamlı düzelme olduğu görüldü. Vertebrave femur T-skorundaki ve femur BMD değerindeki ortalama düzelme bakımından grup 'P' daha iyiydi ve istatistiksel olarak anlamlıfark vardı. Oralbifosfonat grubunda femur T-skorunda alendronat lehine gruplar arasında istatistiksel anlamlı fark olduğu ve parenteral bifosfonat grubunda ise vertebra ve femur T-skorundaki düzelme zoledronat altgrubunda daha iyiydi ve istatistiksel olarak anlamlıydı.

Sonuç: Çalışmamızın sonuçları; postmenopozal OP'nin tedavisinde oral ve parenteral bifosfonatların etkili olduğunu göstermektedir. Bununla birlikte vertebra ve femur T-skorlarında ve femur KMY ortalama düzelme bakımından parenteral bifosfonatlar daha etkili bulundu.

Anahtar kelimeler: DEXA; bifosfonat; Postmenopozal osteoporoz; zolendronik asit.

Introduction

Osteoporosis (OP) is a systemic metabolic bone disease which is characterized by low bone mass and impaired bone microarchitecture and increases susceptibility to fractures[1] [2]. In two large-scale studies conducted recently in our country, the incidence of OP was reported as 12.9-19.6% [3] [4]. Osteoporotic fractures are associated with morbidity and mortality as well as significant social and economic consequences [5]. Practices for prevention, diagnosis and treatment of OP can prevent fractures and their sequelae [6]. Bisphosphonates (BF) are the first-line treatment drugs with proven efficacy in reducing the risk of vertebral, hip and non-vertebral fractures. BFs that have been approved by the US Food and Drug Administration (FDA) for prevention and treatment of OP include alendronate, ibandronate, risedronate and zoledronate [6][7].BF, which is very commonly used in the treatment of OP, binds hydroxyapatite in bone and creates resistance to the action of pyrophosphatases, thus reducing bone resorption. BFs used in OP treatment have oral or parenteral forms. Several studies reported various efficacy and side-effect rates [5][7]. On the other hand, the efficacy and side-effects of selected medication, and the medication adherence of patients are also important [8][9]. However, there are a few studies that compare the efficacy, side-effect and the medication adherence for various forms of BFs [10][11].

In this study, we aimed to compare the efficacy of oral and parenteral BFs used in the treatment of postmenopausal OP.

Material and Methods

Patients aged 65 and older who were diagnosed with postmenopausal OP and treated with oral or parenteral bisphosphonate for 3 years between 2016 and 2019 in the clinics where the authors have worked were included in the study. Medical and demographic data of the patients were recorded. Secondary OP cases and patients meeting with any of the exclusion criteria [5], including those having additional criteria (metabolic, endocrine, neuropsychiatric, malignancy, etc.) or those consuming alcohol, smoking and using a steroid for long-term (≥5 mg and ≥3 months), those being confined to bed, those having implant on bone densitometry scanning region (hip and vertebra), and those discontinued the treatment due to BF intolerance or other serious side-effects, were not included in the study. The results of bone density scanning performed by Lunar-DPX IQ device or the results converted to Lunar values [12] were included in the study. This study was conducted as per the ethical rules stated in the 2013 reversion of the Declaration of Helsinki (1964). The patients were informed that their results are to be used for scientific purposes, and their consents were obtained [Approval of the Ethics Committee of Adana City Hospital was obtained (Date:22.04.2020/ decision no: 803).

The points to consider in posterior-anterior vertebra (L1-L4) and femoral neck (Total) measurements in bone density scanning were determined, and the devices were maintained and calibrated according to the recommendations of the International Society for Clinical Densitometry [13] and the Turkey Association of Nuclear Medicine [14]. Calibration, testing, inspection and phantom measurements of the devices were performed by certified technicians regularly. The heights and weight of the participants were measured without heavy clothes and then they were scanned by Dual-energy X-ray absorptiometry (DEXA). The cases with OP were identified by their T-scores according to the World Health Organization (WHO) criteria. The treatment to be applied was determined according to the patient's preference (tablet or needle), concomitant disorders (BF intolerance due to gastritis, ulcer, etc.), Social Security Institution's (SSI) criteria and the physician's preference. The SSI's reimbursement criteria were considered for the diagnosis and treatments.

The patients were retrospectively divided into two groups according to the treatment they have received. The patients in group O receiving oral BF were administered with [alendronate 70 mg/week (n=25), ibandronate 150 mg/month (n=24)], risedronate 35 mg/week or 150 mg/month (n=23)). In group P receiving parenteral BF, 50 patients were administered with 5 mg zoledronate by 15-min intravenous infusion once a year, and 30 patients were administered with 3 mg ibandronate by IV infusion (IV) every three months. Before the drug administration, the biochemical test results of the patients were evaluated, and no drugs were administered to those with renal dysfunction and the resulting side-effects were recorded. Also, vitamin d replacement treatment was not administered before the treatment, but all the patients on BF treatment were given 800 IU/day of vitamin D3, 1,200 mg/day of calcium.

The patients were called for periodic checks. Any increase or decrease in the patients' complaints and any side effects were noted. Also, the patients underwent a comprehensive physical examination. The results of the second-year treatment of 160 patients who were treated regularly and could be followed-up for at least 2 years were evaluated. The bone mineral density (BMD) and T-scores were evaluated by DEXA.

Statistical Analysis

The obtained data were classified numerically and categorically and saved in Excel. The pre-treatment and second-year treatment results of the patients were analyzed statistically. The descriptive statistics were given as mean±standard deviation and percentage. The conformity of the data with normal distribution was determined by Kolmogorov-Smirnov test. In significance analyses: In group comparisons, the mean improvement rates in BMD and T-score were compared using the independent t-test. In subgroup comparisons, the Kruskal-Wallis test was used in the comparison of more than two groups, while the Mann-Whitney U test was used in post-hoc analysis and/or in comparison of two groups. In intra-group comparisons, the treatment utilization rates were evaluated by comparing to baseline values and control values using the Paired t-test. The p values below 0.05 ($p<0.05$) were considered statistically significant.

Results

No statistically significant difference was found between group O (n=80) and group P (n=80) in terms of mean age (68.3±5.26 and 72.85±5.37) and mean body mass index (BMI) (27.56±5.54 and 28.85±5.48) (p=0.459 and p=0.413, respectively).Both groups showed significant improvement in vertebral and femoral BMD and T-scores at the end of 2-year treatment compared to baseline (Paired t-test; Table 1). It was seen that the patients have benefited from both treatment methods.

Table 1. Changes in T-scores in treatment Tab

Parameters	Group 1 n=80 (oral bisphospho-nate)	Group 2 n=80 (parenteral bisphospho-nate)	p*
L1-L4 t score 1. End of year	-3.156±0.87	-2.785±1.02	
L1-L4 t score 2. End of year	-2.952±0.92	-2.125±0.79	
p**	0.000	0.000	
L1-L4 t score change	0.312±0.07	0.698±0.12	0.003
Vertebral BMD	0.698±0.15	0.912±0.09	
Vertebral BMD 2. End of year	0.792±0.13	0.974±1.17	
p**	0.002	0.005	
Change in Vertebral BMD	0.057±0.018	0.089±0.16	0.064
Femoral neck T-score	-2.417±1.21	-2.428±1.12	
Femoral neck T-score End of 2nd year	-2.213±1.07	-1.659±0.89	
p**	0.001	0.000	
Femoral neck Change in T-score	0.179±0.07	0.812±0.09	0.000

*Independent Samples t-test, **Paried t-test

On the other hand, the mean improvement in vertebral and femoral T-score was better in group P and there was a statistically significant difference between the groups (p*=0.003 and p=0.000, respectively; Table 1). Nevertheless, no significant difference was found between the groups in terms of vertebral BMD (p=0.064; Table 1).In subgroup comparisons, although there was a statistically significant difference in femoral neck T-score in favor of alendronate in the oral BF group (p=0.042; Table 2), no statistically significant difference was found between oral sub-groups in terms of improvement in vertebral T-score and vertebra values (p=0.106, p=0.878, respectively; Table 2). In sub-group comparisons, there was also no significant difference between the groups in terms of age and BMI (Table 2, 3).

Table 2. Sub-group comparison in group O

Parameters	Alendronate (n=30)	Ibandronate (n=30)	Risedronate (n=20)	p*
Age (year; significance ± sd)	70.12±4.03	73.25±6.48	72.36±6.97	0.571
Body mass index (significance ± sd)	27.13±5.97	27.04±5.14	28.42±6.03	0.617
Change in L1-L4 t-score	0.506±0.08	0.197±0.07	0.325±0.08	0.106
Change in Vertebral BMD	0.123±0.06	0.0336±0.01	0.049±0.01	0.878
Change in femoral neck T-score	0.302±0.07	0.2756±0.12	0.025±0.07	0.042**

*Kruskal-Wallis test, **Aledronate group showed significantly greater improvement (post-hoc Mann-Witney U test), SD: standard deviation

In the parenteral BF group, the improvement in vertebral and femoral T-score was better in the zoledronate sub-group and statistically significant (p=0.043 and p=0.035, respectively; Table 3). On the other hand, although the mean improvement in vertebra value was better in the zoledronate group, no statistically significant difference was found (p=0.088, Table 3).

In this study, the results of the patients who discontinued the treatment due to serious adverse effects other than tolerable gastrointestinal side effects of oral BFs and symptoms like influenza that are seen after IV administration of parenteral BFs and are tolerable by patients were not evaluated

Table 3. Sub-group comparison in group P

Parameters	Zoledronate (n=40)	Ibandronate (n=40)	p*
Age (year; significance ± sd)	76.36±5.78	75.57±5.42	0.597
Body mass index (significance ± sd)	26.45±5.36	26.38±4.95	0.390
L1-L4 t score change	0.890±0.15	0.606±0.10	0.043
Change in Vertebral BMD	1.128±0.22	0.495±0.09	0.088
Change in femoral neck T-score	0.310±0.29	0.093±0.03	0.035

*Mann-Witney U test, SD: standard deviation

Discussion

The most used in OP scanning and diagnosis is BMD measurement in hip and lumbar region with DEXA method. According to the diagnosis criteria of WHO (World Health Organization), OP is diagnoses with a T-score ≤ −2.5 [6][13][15]. According to the treatment expenses reimbursement system applied in our country, OP treatment is evaluated based on the DEXA results, thus the BMD and T-scores obtained by DEXA measurements are important for diagnosis and treatment continuity [6][16]. In postmenopausal OP treatment, various drugs with proven efficacy in reducing the risk of fractures are used. The most commonly used agents in the pharmacological treatment of OP are BFs such as alendronate, risedronate and ibandronate, and raloxifene, denosumab and parathyroid hormone, as selective estrogen receptor modulator [7]. Antiresorptive and anabolic agents used in OP treatment have different doses and modes of administration. However, BFs are still basic treatment agents in OP [7][11].

In this retrospective cross-sectional study, using the vertebral and femoral BMD and T-scores, we evaluated the effectiveness of oral (alendronate, ibandronate and risedronate) or parenteral (zoledronate, ibandronate) BF treatment protocol administered to 160 patients, who were diagnosed with postmenopausal OP according to the WHO criteria considering the T-scores determined using DEXA, and followed-up for two years.

A recent systematic review and meta-analysis study, where the

cost-effectiveness of oral and parenteral drugs in OP treatment, reported that oral aledronate and parenteral zoledronate are the best first-line treatment option in postmenopausal OP. This study also reported that there was no statistically difference between the existing drugs in terms of the efficacy in preventing hip fractures. Another recent meta-analysis on the efficacy of different BFs in preventing osteoporotic fracture reported that alendronate and zoledronic acid are the most effective agents in preventing femoral, vertebral and non-vertebral osteoporotic fractures [11].

In our study, both groups showed significant improvement in vertebral and femoral neck BMD and T-scores at the end of a 2-year treatment compared to baseline (Table 1). It was seen that the patients have benefited from oral or parenteral BF treatment methods. On the other hand, the mean improvement in vertebral and femoral neck T-score was better in group P and there was statistically significant difference between the groups (Table 1). Group P showed better improvement in femoral neck BMD value, and there was a statistically significant difference between the groups, however, no significant difference was found between the groups in terms of vertebra BMD values (Table 1).

Although there are many oral BF compounds, the 3rd generation BFs (neridronate, alendronate, olpadronate, risedronate, ibandronate) are most preferred today. Studies have proven that BFs are effective in the treatment of women with postmenopausal OP [7]. A meta-analysis showed that alendronate reduced hip fractures by about 55% in women with postmenopausal OP [17]. A reduction in vertebral fractures was seen by clinical observations at the end of the first year of the treatment. A meta-analysis study reported that protection from hip fracture was evident after 18 months of treatment [18]. Its efficacy in preventing hip fractures was significant in women with and without a vertebral fracture after the 18th month, which has maintained for 36 months[18] [19] In a study conducted by Aslan et al. [20] to evaluate the efficacy of 6 different drugs (alendronate, ibandronate, risedronate, calcitonin, strontium and raloxifene) in 144 patients with postmenopausal OP based on vertebral and femoral BMD and T-scores, it was reported that aledronate has a significant effect, especially on vertebral BMD and T-scores.

In subgroup comparisons under our study, there was a statistically significant difference in femoral neck T-score in favor of alendronate in the oral BF group (Table 2). However, there was no statistically significant difference between oral sub-groups in terms of improvement in vertebral T-score, vertebral and femoral neck BMD values (Table 2).

Zoledronate used in OP treatment as a parenteral BF is an FDA-approved agent with proven efficacy in preventing new fractures after an osteoporotic hip fracture. In HORIZON-PFT study with a large series to determine the efficacy of zoledronic acid in postmenopausal OP, the patients were administered with zoledronic acid at baseline, 12 and 24 months. The patients were followed up for 2 years and compared with the placebo group [21]. The primary endpoint of this study was a new vertebral fracture and hip fracture. In the zoledronic acid group, the risk of morphometric vertebral fracture was reduced by 70% and the risk of hip fracture was reduced by 41% within 3 years [22](25). In the Dosing Intravenous Administration (DIVA) study, lumber BMD increased compared to baseline with dual IV (3 mg every 3 months, 2 mg every 2 months) ibandronate administration (5.1% and 4.8%), while the lumber BMD increased by 3.8% compared to baseline with a regimen of 2.5 mg of oral ibandronate daily [23].

A study with 82 patients who were administered with parenteral zoledronate and ibandronate reported that there was a statistically significant increase in BMD compared to baseline in both groups at the end of 1-year follow-up, however, there was no significant difference between the groups in terms of mean BMD values at the end of 1-year follow-up. Consequently, the authors reported that the BMD values significantly improved in OP patients receiving zoledronate and ibandronate, and there was no significant difference in terms of efficacy and experienced side-effects [11].

In our study; in the parenteral BF group, the improvement in vertebral and femoral neck T-score was better in the zoledronate sub-group and statistically significant (Table 3). On the other hand, although the mean improvement in vertebral and femoral BMD value was better in the zoledronate group, there was no statistically significant difference (Table 3).

At least 1000 mg of calcium and 600 IU of vitamin D are recommended daily in all prevention and treatment strategies for OP. Despite recent controversies regarding the safety of calcium and the optimal dose of calcium and vitamin D, calcium and vitamin D are still an important part of bone health [7]. In our study, all the patients were administered with 800 IU/day of vitamin D3 and calcium of 1200 mg/day.

Limitations of the Study

The shortness of the follow-up period may be a limitation.

Another limitation is the fact that we have evaluated the efficacy of drug groups with the T-score of BDM determined only using DEXA. Although it is not the case in this study, the bone resorption markers and vitamin D levels are important markers being used in follow-up [16][20]. On the other hand, the evaluation of treatment-related side effects was not included in this study. Upper gastrointestinal symptoms are often seen in oral BF treatment, while symptoms like temporary influenza are commonly seen in parenteral BF treatment with nitrogen [5][20]. The diversity of DEXA devices used in BMD measurements may cause differences in BMD measurements made in different regions. Also, different field and density determination algorithms and different calibration practices used by manufacturers make standardization studies further difficult. Finally, although DEXA has been used for many years for diagnostic and therapeutic purposes in our country, the standardization of operator (technician) training can lead to errors in the acquisition, analysis and interpretation of the scan [24]. These points also apply to our study and may have affected the results of our study.

Conclusion

This study concluded that oral and parenteral bisphosphonates are effective in the pharmacological treatment of postmenopausal OP. Nevertheless, parenteral BFs were found to be more effective in terms of mean improvement in vertebral and femoral neck T-scores. Also, it was found that aledronate among oral BFs provided significantly better improvement in femoral T-score, and zoledronate among parenteral BFs showed better improvement in both femoral neck and vertebral T-scores. More comprehensive, long-term comparative studies are needed on this subject.

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