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Original Research

Bazedoxifene effects on osteoprotegerin, insulin-like growth factor, tumor necrosis factor and bone mineral density

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Abstract: To observe the clinical effect of estrogenic drugs (Bazedoxifene) on bone targeting in the treatment of osteoporosis and explore its mechanism. Methods:112 patients with postmenopausal osteoporosis who received Bazedoxifene drugs in our hospital from January to December 2018 were collected as a study group, and 56 patients treated with calcium alone were collected as a control group. the risk of adverse events such as bone mineral density, osteoprotegerin (OPG), insulin-like growth factor (IGF), tumor necrosis factor (TNF-α), and fracture after treatment were analyzed before and after treatment. Results: There was no significant difference in the mean lumbar positive position (L2-4) and right femoral neck bone density and OPG, IGF, TNF-α level between the two groups before treatment (P>0.05). The total effective rate of clinical treatment in the study group was 88.39%, the control group was 23.21%, the difference between the two groups was statistically significant (P<0.05). After treatment, the mean lumbar positive position (L2-4) and the right femoral neck bone density and OPG, IGF in the study group were higher than those in the control group, lower than those in the control group (P<0.05). the occurrence of adverse events such as fracture, spinal deformation and fatigue in the study group after 12 months of treatment was significantly lower than that in the control group (P<0.05), but there was no significant difference in the occurrence of hot flashes and venous thromboembolism between the two groups (P>0.05). Conclusion: Bazedoxifene is an effective drug for the treatment of postmenopausal osteoporosis. It can not only prevent the rapid loss of bone mass, effectively relieve the symptoms of menopause, but also improve bone density and reduce the risk of fracture.

Key words: Estrogen; Bazedoxifene; Osteoporosis; Clinical effect.

Introduction

Osteoporosis is the most common in the elderly group (1, 2). It is a bone disease characterized by bone mass loss and bone microstructure destruction, resulting in increased bone brittleness. It can reduce the quality of life of patients, cause seriously deform the spine and disability fracture, lead to life cannot be self-care, and bring heavy economic burden to family and society. Currently, the clinical treatment of osteoporosis is still dominated by drugs (2, 3). With the deepening of the research on the pathogenesis of osteoporosis and the continuous development of new anti-osteoporosis drugs, a variety of targeted bone therapy drugs are widely used in osteoporosis patients (4). Since estrogen deficiency is a major characteristic of postmenopausal women, estrogen replacement therapy is one of the main therapeutic measures for postmenopausal patients (5). Moreover, bone is the target of estrogen, and estrogen deficiency can have a direct effect on bone tissue (6). Related studies have shown that exogenous estrogen supplementation can exert anti-osteoporosis effects through cell receptor pathways (such as estrogen receptors directly acting on the surface of osteoblasts and osteoclasts) (7-8). Bazedoxifene (BX) is as a third-generation selective estrogen receptor modulator, there are still few reports on the clinical effects and related mechanisms of BX in the treatment of postmenopausal osteoporosis patients. Therefore, this paper observed the clinical effects of BX in the treatment of postmenopausal osteoporosis patients. The reports are as follows.

Materials and Methods

General information

A total of 112 patients with postmenopausal osteoporosis who received Bazedoxifene in our hospital from January to December 2018 were collected as the research group. Inclusion criteria were as follows: (a) meeting the diagnostic criteria of osteoporosis (9), T value ≤-2.5; (b) Are postmenopausal women; Menopause time ≥2 years; (3) with primary back pain, knee hip pain and other peripheral bone pain symptoms; (4) All the patients gave informed consent and cooperated with the follow-up. Exclusion criteria: (a) secondary osteoporosis;(b) severe cardiovascular disease or liver and kidney function impairment;(c) with a tumor or other metabolic diseases; (d) Long-term use of immunosuppressive agents, glucocorticoids. Fifty-six patients treated with calcium alone were collected as the control group. This study was approved by the academic committee of our hospital. There was no statistically significant difference in age, body mass index, disease course and other general information between the two groups (P > 0.05) (Table 1), indicating comparability.

Table 1. Comparison of general data between the two groups.

Group	Age	Body mass index(kg/m2)	Course of disease (year)
Observation (n=112)	49~73 (63.52±5.76)	19.25~27.12 (24.15±3.12)	1~5 (2.68±1.24)
Control (n=56)	52~70 (62.63±4.36)	19.17~27.01 (24.01±3.08)	1~5 (2.45±1.20)
t	1.019	0.275	1.145
P	0.309	0.783	0.253

Methods

The control group was given calcium treatment, and calcium erqi D3 tablets were selected (manufacturer: Wyeth Pharmaceutical co., LTD., national drug approval (H10950029). Each tablet contains vitamin D3 125U+ calcium carbonate 0.6g, taken orally, 2 times/day, 1 tablet each time. The study group was given calcium hormone therapy, and calcium was given erqi D3 tablets (manufacturer: Wyeth pharmaceutical co., LTD., national drug approval (H10950029). Each tablet contains vitamin D3 125U+ calcium carbonate 0.6g), taken orally, 2 times/day, 1 tablet each time. Viviant Tablets (BAZEDOXIFENE ACETATE) was selected as hormone (manufacturer: Pfizer; Specification: 20 mg/tablet, 100 tablets/box), taken orally, once per day, 1 tablet each time. Nutrition during treatment doctors give dietary guidance: eating calcium-rich foods such as tofu, small high calcium milk, dried small shrimps, seaweed, kelp, etc., increase the light time, guarantee the activity of the 1 h (jogging, gymnastics, tai chi exercise and do less the trunk flexion, rotation and other movements), no smoking, and limit alcohol consumption.

Observation indicators

Observation of the therapeutic effect of patients: visual analogue scale (VAS) was used to evaluate the pain degree of patients before and after 12 months of treatment, including resting lumbago back pain, rollover pain, anterior flexion and posterior extension pain. Excellent: VAS score decreased ≥80%; Good: VAS score decreased by 60% ~ < 80%; Average: VAS score decreased by 40% ~ < 60%; Poor: VAS score decreased < 40%. Total effective rate = (excellent + good) cases/total cases *100%.

The risk of bone mineral density (BMD), osteoprotegerin (OPG), insulin-like growth factor (IGF), tumor necrosis factor (TNF-α) and other adverse events before and after treatment were observed. Bone mineral density test: before and after 12 months of treatment, dpx-md dual-energy X-ray instrument (Madison, USA) was used to measure the lumbar orthosis (l2-4) and bone mineral density (BMD) of the right femoral neck of patients in the two groups.5mL venous blood was collected on an empty stomach and centrifuged at a speed of 3500rpm for 10 minutes. After centrifugation, the serum was collected and stored in a refrigerator at -20℃ for inspection. Serum OPG detection: enzyme-linked immunosorbent assay was used through human bone protectant ELISA kit purchased from Jiangsu Jingmei biotechnology co., LTD. Serum IGF detection: igf-1 release kit from Tianjin Jiuding Medical Biological Engineering Co., LTD. Serum TNF-α assay: human TNF-α assay kit from Shanghai Kanglang Biotechnology co., LTD.

Statistical methods

Spss20.0 statistical software was used, and the counting data were expressed by the rate (n%), and the χ^2 test was used. The measurement data were expressed as mean ± standard deviation ($\bar{x}$ ±s), and the comparison of the two mean values between the two groups by t-test showed that P < 0. 05 indicated a statistically significant difference.

Results

Comparison of treatment effect between the two groups

The total effective rate was 88.39% in the study group and 23.21% in the control group and the difference between the two groups was statistically significant (P < 0.05) (Table 2).

Bone mineral density before and after treatment in the two groups

There was no statistically significant difference between the mean lumbar orthosis (l2-4) and the bone mineral density of the right femoral neck between the two groups before treatment (P > 0.05). After treatment, the average lumbar orthosis (l2-4) and right femoral neck bone mineral density in the study group were higher than those in the control group, with statistically significant differences (P < 0.05) (Table 3, Figure 1).

There was no statistically significant difference in average levels of OPG, igf-1 and TNF-α between the two groups before treatment (P > 0.05). After treatment, the average OPG and igf-1 in the study group were higher than those in the control group, while TNF-α was lower than those in the control group, with statistically significant differences (P < 0.05) (Table 4).

Comparison of fractures and other adverse events after treatment between the two groups

After 12 months of treatment, the incidence of fractures, spinal deformation, fatigue and other adverse events in the study group was significantly lower than

Table 2. comparison of treatment effect between the two groups [n (%)].

Group	Excellent	Good	Average	Poof	Total effective rate
Observation(n=112)	58(51.78)	41(36.61)	11(9.82)	2(1.79)	99(88.39)
Control(n=56)	3(5.35)	10(17.86)	17(30.36)	26(46.43)	13(23.21)
χ^2					71.371
P					<0.001

Table 3. Comparison of a lumbar orthosis (l2-4) and bone mineral density of the right femoral neck between the two groups (g/cm2, $\bar{x}$ ±s).

Group	Lumbar orthosis (L2-4)		Right femoral neck	
	Before	After	Before	After
Observation(n=112)	0.57±0.06	0.77±0.06	0.55±0.06	0.74±0.07
Control(n=56)	0.58±0.05	0.63±0.07	0.56±0.07	0.61±0.06
t	1.074	13.472	0.962	11.881

Table 4. Comparison of serum OPG, igf-1 and TNF-α levels between the two groups before and after treatment (±s).

Group	OPG (pmol/L)		IGF-1 (μg/L)		TNF-α(pg/ml)	
	Before	After	Before	After	Before	After
Observation(n=112)	3.58±0.42	8.82±1.33	170.38±25.17	271.62±32.59	16.38±2.21	11.18±2.07
Control(n=56)	3.61±0.45	4.37±0.53	174.11±26.15	206.35±29.86	15.89±2.11	15.20±2.13
t	0.426	24.073	0.893	12.584	1.375	11.750
P	0.670	<0.001	0.372	<0.001	0.171	<0.001

Table 5. Comparison of adverse events after treatment between the two groups [n (%)].

Group	Fractures	Spinal deformation	Fatigue	Hot flashes	Venous thromboembolism
Observation(n=112)	1 (0.89)	2 (1.78)	4 (3.57)	7 (6.25)	2 (1.78)
Control(n=56)	4(7.14)	7(12.50)	8(14.28)	1(1.78)	0(0)
χ^2	5.050	8.453	6.462	1.641	1.012
P	0.025	0.004	0.011	0.200	0.314

that in the control group, with statistically significant differences (P < 0.05), but there was no statistically significant difference in the occurrence of hot flashes and venous thromboembolism between the two groups (P > 0.05) (Table 5).

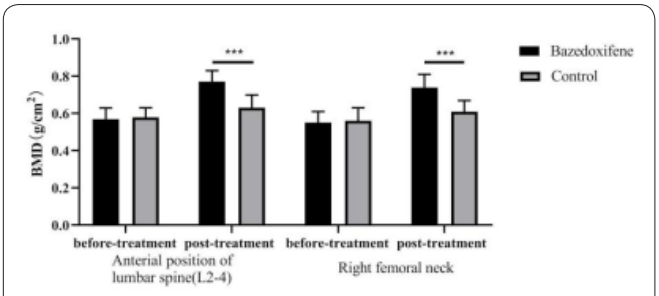

Figure 1. Comparison of serum levels of OPG, igf-1 and TNF-α between the two groups before and after treatment.

Discussion

The ovarian function of postmenopausal women gradually decreased, and the estrogen level significantly decreased (10). As estrogen plays an important role in regulating bone metabolism (11), postmenopausal women's bone metabolism is affected by the decline of estrogen. The metabolic imbalance of bone resorption and bone generation cannot effectively inhibit osteoclasts. Osteoclasts are unable to effectively inhibit, osteocytes are rapidly decomposed and absorbed, leading to a decline in bone quality and bone density, which causes osteoporosis (12). At present, hormone therapy is a commonly used treatment for postmenopausal osteoporosis. By supplementation of exogenous estrogen, hormone therapy can improve the level of estrogen in the body, thus restoring the balance of bone metabolism and improving bone mineral density to a certain extent (13). However, the therapeutic effect of BX as a new generation of selective estrogen receptor modulators in postmenopausal osteoporosis patients has been rarely reported, so this paper analyzed the clinical effect of BX in the treatment of postmenopausal osteoporosis patients after 12 months.

The results of this study showed that after 12 months of BX treatment, the mean lumbar orthosis (l2-4) and bone density of the right femoral neck and the total clinical response rate of postmenopausal osteoporosis patients were significantly higher than that of calcium treatment (P < 0.05), suggesting that BX could effectively improve symptoms and improve bone density in patients. After treatment, OPG and igf-1 in the study group were significantly higher than those in the control group, while TNF-α was lower than those in the control group (P < 0.05). OPG is a new member of the tumor necrosis factor (TNF-α) receptor family, also known as osteoclast inhibitor (14). It is mainly secreted by osteoblasts and binds to the nuclear factor B receptor activating factor ligand (RANKL) to block the signaling pathway of osteoclasts, thus inhibiting the destruction of osteoclasts to bone (15). Related studies have shown that (16), OPG indirectly inhibits the formation and activation of osteoclasts by binding to OPGL, thus playing an anti-osteoporosis role. After treatment with selective estrogen receptor modulator BX, the OPG and bone mineral density of the study group were significantly improved, indicating that BX inhibited the formation and activation of osteoclasts by improving the level of OPG, and effectively inhibited the absorption of osteoclasts to the bone, thus improving bone mineral density. IGF is a polypeptide protein similar to insulin in molecular structure, also known as a growth-promoting factor. The Igf-1 can promote the synthesis of bone matrix, inhibit the catabolism of bone, prevent the loss of calcium in bone, and maintain bone mass balance (17-18). In this study, after treatment with BX, igf-1 was significantly upregulated, indicating that BX could

promote the secretion of igf-1 *in vivo*, thereby promoting the proliferation of osteoblasts and effectively preventing and treating osteoporosis. Related studies have found that TNF-α may inhibit osteoblast differentiation (19), and its increased content can promote osteoclast apoptosis (20). In this study, after treatment with BX, TNF-α significantly decreased, indicating that BX could reduce the level of TNF-α, thus reducing the rate of apoptosis of osteoblasts and normalizing the differentiation of osteoblasts, so as to effectively prevent and treat osteoporosis.

In summary, bardoxifene is an effective drug for the treatment of postmenopausal osteoporosis. It can not only prevent the rapid loss of bone mass, effective relief of osteoporosis back pain, systemic bone pain and other symptoms but also can improve bone density and reduce the risk of fracture.

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