Efficacy of combined medication of risedronate sodium and selective estrogen receptor modulator on the postmenopausal osteoporosis

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Abstract: To evaluate the efficacy of combined medication of risedronate sodium and raloxifene, a selective estrogen receptor modulator (SERM) on the postmenopausal osteoporosis (PMOP). PMOP patients underwent the combined medication of risedronate sodium and raloxifene (SERM, Treatment group), or only medication of risedronate sodium (Control group). After medication, more significant increases were observed in the bone densities of the lumber vertebra (L_{1-4}) and the neck of left femur of patients in the treatment group. Simultaneously, the levels of estrogen and progesterone in serum decreased sharply in the treatment group. After treatment, P1NP and β-CTX levels in serum decreased significantly in two groups in comparison with the levels prior to treatment, with evident elevations in the levels of BAP and BGP; similarly, ameliorations in the treatment group were much more evident than those in the control group. In addition, significant declines were identified in the VAS scores of two groups after treatment when comparing to the scores prior to the treatment, and the decline in the treatment group was more evident than that in the control group. Combined medication of risedronate sodium and SERM (raloxifene) performs better in treatment of osteoporosis than the single use of risedronate sodium, without the deterioration of adverse effect of medication.

Keywords: Risedronate sodium, estrogen replacement therapy, raloxifene, postmenopausal osteoporosis, bone mineral density.

INTRODUCTION

Postmenopausal osteoporosis (PMOP), as a common aging-related disease, usually leads to the peripheral pains, chest pain, back pain or even height shortening, with manifestation of low bone mass or damage to the microstructure of bone tissues. Thus, the increased fragility of bones makes them more susceptible to the fracture. It is estimated that 50% of the postmenopausal women experience the osteoporosis-caused fracture in their life (Sun *et al.,* 2016). As elder population suffers a high risk of fracture-caused morbidity, or even death, timely treatment of osteoporosis is critical (Chavassieux *et al.*, 2015). At present, multiple drugs have been used for prophylaxis and treatment of PMOP, effects of which on the bone mineral density (BMD) and bone transformation indicator are associated with the anti-fracture efficacy in clinical trials, consisting of the anti-bone absorption drugs, such as diphosphonates (*e.g.* alendronate sodium or risedronate sodium), Salmon Calcitonin Nasal Spray and selective estrogen receptor regulator (SERM, including raloxifene) (Lambertini *et al.*, 2017). The controlled clinical trials with PMOP women as subjects (Chavassieux *et al.*, 2015) showed that risedronate sodium, salmon calcitonin and raloxifene reduce the risk of vertebral fracture remarkably, and all of them are able to increase the BMD by varying degrees.

For women with severe osteoporosis, or responding poorly to the single medication, combined medication may generate more benefit for them (Lambertini *et al.*, 2017; Cummings *et al.*, 2017). Hence, we sought to explore the efficacy of combined medication on PMOP women, so as to provide the clinical basis for availability of combined medication.

MATERIALS AND METHODS

Data collection

From June 2018 to May 2019, we enrolled 140 PMOP patients that were diagnosed and admitted to Jingzhou Chinese medicine hospital of Hubei province. Inclusive criteria: a) Patients aged between 55 and 65 years old, with at least a 5-year interval from last menopause; b) Patients who were diagnosed according to the diagnostic criteria of osteoporosis by WHO, *i.e.* T ≤-2.5 for diagnosis. Exclusive criteria: a) Patients with the history of bone metabolism disease; b) Patients with the medication history of drugs affecting the bones or metabolism, such as diphosphonate, calcium or Vitamin D; c) Patients with deficiency in Vitamin D; d) Patients with problems in sexual hormones, or the history of hormone replacement therapy; e) Patients with the coagulopathy or thromboembolic diseases; f) Patients with cardiovascular diseases or cerebrovascular diseases; g) Patients with the history of drug abuse, smoking or alcohol, or the adverse responses or effect of drugs during the study; h) Patients

that were unable to continue on the study. Eligible women were randomized into the control group and treatment group, with 70 subjects in each group. In the control group, patients had menopause aged between 46 and 57 years, averaged at (51.47±2.14) years, while those aged between 55 and 64 years, averaged at (61.78±3.47) years; disease course of PMOP ranged from 1 to 10 years, with an average of (5.24±2.39) years; body mass index of patients ranged from 20.24 to 30.81 kg/m^2, with an average of (25.17±4.73) kg/m^2. In the treatment group, patients had menopause aged between 45 and 56 years, averaged at (51.02±2.11) years, while those aged between 55 and 65 years, averaged at (61.99±3.52) years; disease course of PMOP ranged from 1 to 10 years, with an average of (5.18±2.35) years; body mass index of patients ranged from 20.08 to 30.93 kg/m^2, with an average of (25.08±4.67) kg/m^2. Comparisons of the age, menopausal age, disease course or BMI showed no statistically significant difference (*P*>0.05), suggesting the comparability of the data. This study had gained the approval from the Ethic Committee of the Jingzhou Chinese medicine hospital of Hubei province.

Treatment

Patients in two groups were guided to take outdoor exercise, including Tai Ji or walking, 1 to 2h per day, have balanced diet (taking food rich in calcium and low in salt, with appropriate volume of proteins, and guaranteeing the daily intake of vitamin D at about 10μg (400 IU). For patients in the control group, they took risedronate sodium tablets (Hua Xin Pharmaceutical Co., Ltd, SFDA Approval No.: H20080127, 5 mg × 8 s) orally, one tablet per day. Patients in the treatment group underwent the combined medication of risedronate sodium tablet and raloxifene (Jiangsu Hengrui Medicine Co., Ltd, SFDA Approval No.: H20050899, 60 mg × 7 tablets), one tablet per day. Treatment was performed for 12 months in two groups.

Observation of indicators

Dual-Energy X-Rays Absorptiometry ((DPX-L, GE Lunar, USA) was employed to detect the bone mineral densities of L_1 to L_4 lumber vertebrae and the left-sided femur neck of the subjects respectively prior to the treatment and at 12 months after treatment, with the error coefficient within 1.5%. At the beginning and the end of treatment, fasting blood samples were collected from all subjects for centrifugation at 1000 r/min for 10 min, followed by storage at -70°C. All evaluations were performed in the laboratories. Radioimmunoprecipitation (ELISA, Ostase, Hypritech, San Diego, CA, USA) was applied to determine the serum levels of bone alkaline phosphatase (BAP) and osteocalcin (OCN), and the changes in the levels of P1NP and βCTX in serum. Enzyme-linked immunosorbent assay (ELISA) was carried out to measure the levels of progesterone, estradiol and cortisol in serum (ELISA, Ostase, Hypritech, San Diego, CA,

USA). Furthermore, visual analogue scale was also adopted to evaluate the pains of patients, and simultaneously, the side effect of drugs was observed in the subjects during medication.

STATISTICAL ANALYSIS

All data were analyzed by using the SPSS 19.0 software. Measurement data were presented in form of mean ± standard deviation, and compared by using the *t* test. Differences in comparison of the indicators before and after treatment were identified by chi-square test and One-way ANOVA. *P* <0.05 suggested that the difference had statistical significance.

RESULTS

Comparison of the VAS scores and BMDs of the lumber vertebrae and hip before and after treatment between two groups

After treatment, VAS scores of patients in two groups were significantly decreased when comparing to those before treatment (*P*<0.05), with significant increases in the BMDs of lumber vertebra (L_{1-4}) and the neck of left femur (*P*<0.05), and the changes in the indicator above in the treatment group were more evident than those in the control group (*P*<0.05; table 1).

Comparisons of the hormone levels before after treatment between two groups (estrogen, progesterone and cortisol)

After treatment, the levels of estrogen and progesterone in serum decreased sharply in the treatment group, with an evident increase in the level of cortisol in comparison with the levels before treatment (*P*<0.05), whereas no significant changes were identified in indicators above in the control group (*P* >0.05; table 2).

Comparison of the indicator levels of bone metabolism before and after treatment between two groups (P1NP, β-CTX, BAP and BGP)

After treatment, P1NP and β-CTX levels in serum decreased significantly in two groups in comparison with the levels prior to treatment, with evident elevations in the levels of BAP and BGP (*P*<0.05); similarly, ameliorations in the treatment group were much more evident than those in the control group (*P*<0.05).

Comparison of the adverse events of patients between two groups

During treatment, 5 patients presented with the nausea, fatigue, anorexia and dizziness in the control group, while 7 presented with the nausea, fatigue, anorexia and dizziness in the treatment group. Symptomatic treatment resolved the symptoms above. Differences in the incidence rate of adverse events showed no statistical significance (*P* >0.05).

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Table 1: Comparison of the VAS scores and BMDs of the lumber vertebrae and hip before and after treatment between two groups (mean ± standard deviation)

Group		VAS scores	BMD of $L_{1\text{-}4}$ (g/cm^2)	BMD of left femur neck (g/cm^2)
Treatment group	Before treatment	8.7±2.5	0.803±0.093	0.743±0.035
	After treatment	1.8±0.6[*#]	0.898±0.081[*#]	0.791±0.044[*#]
Control group	Before treatment	8.5±2.3	0.802±0.062	0.745±0.035
	After treatment	2.7±0.9[*]	0.873±0.077[*]	0.776±0.030[*]

Table 2: Comparisons of the levels of estradiol, progesterone and cortisol before after treatment between two groups (mean ± standard deviation)

Group		Progesterone (nmol/L)	Estradiol (ng/L)	Cortisol (IU/L)
Treatment group	Before treatment	7.55±1.63	372.28±188.83	402.22±122.24
	After treatment	4.25±0.85[*#]	333.64±112.55[*#]	598.33±183.34[*#]
Control group	Before treatment	7.52±1.57	371.59±187.44	401.17±122.25
	After treatment	6.35±1.45	154.35±82.29	412.27±126.45

Table 3: Comparison of the indicator levels of bone metabolism before and after treatment between two groups (P1NP, β-CTX, BAP and BGP)(mean ± standard deviation)

Group		P1NP(IU/L)	β-CTX(IU/L)	BAP(U/L)	BGP(μg/L)
Treatment group	Before treatment	49.35±16.55	0.58±0.30	12.99±3.73	6.65±1.36
	After treatment	17.37±4.90[*#]	0.14±0.05[*#]	19.35±6.88[*#]	10.24±3.65[*#]
Control group	Before treatment	48.17±16.12	0.59±0.33	13.04±3.63	6.63±1.38
	After treatment	25.24±6.66[*]	0.22±0.05[*]	16.33±6.04[*]	8.68±3.44[*]

Note: [*] $P <0.05$ *vs.* before treatment; [#] $P <0.05$ *vs.* control group.

DISCUSSION

Results of this study showed that compared to the baseline data of the PMOP women, single medication of risedronate sodium or combined medication of risedronate sodium and raloxifene could enhance the BMDs of lumber vertebrae and femoral neck, while slow down the bone transformation rate evidently within 12 months. Furthermore, combined medication exhibited more evident changes in BMD and the indicators of bone metabolism than the single medication. Efficient regulation of the bone absorption is taken as the golden criteria for evaluating the efficacy of anti-bone absorption treatment. Nevertheless, the high price of the anti-absorption reagent and difficulty underlying in the execution in the advanced stage contribute to the lower frequency of clinical application (Cummings *et al*., 2017). Results of the clinical trials and the pathological understandings towards the fragility of the bones support the use of BMD and biochemical indicators of bone as the indicators of the clinical efficacy (Qaseem *et al.* 2017). Bone strength, as the indicator, can be used to evaluate the bone structure, rotation, damage accumulation, mineralization and matrix. In this study, the reduction of bone transformation indicators is similar to the published results (Allen *et al.*, 2017). On the basis of the results above, we found that combined treatment may perform better than the single treatment. However, the exact efficacy of anti-reabsorption reagent on the control of

bone transformation rate remains unclear yet. Excessive bone transformation further increases the possibility of bone microdamage, malformation accumulation and augmentation of bone fragility. According to the morphometric study of bone tissues (Qaseem *et al.* 2017), it has been evidenced that combined treatment of anti-absorption treatment is irrelevant with the changes affecting the bone mass.

Allen *et al.* (Allen *et al*., 2017) performed the postmortem analysis over the risk of fracture for patients raloxifene for 4 years (60 mg/day), and found a 39% reduction in risk of one or multiple new-onset vertebral fracture (RR: 0. 64; 95%CI: 0.53～0.76), but no decline in the risk of non-vertebra fracture. A 2-year study (Vandenbroucke *et al*., 2017) revealed that co-administration of estrogen and diphosphonate could further elevate the BMD when comparing to those with single administration of estrogen or diphosphonate. In addition, co-administration also had a sharp decrease in the number of fracture cases. Theoretically, co-administration of estrogen and diphosphonate serves as a more ideal strategy for treatment of osteoporosis, which, however, was not ever recommended as HRT for treatment of PMOP in elder women after the investigation of WHI.

In this study, patients tolerated all therapies well, and the difference in the incidence rate of adverse events among the patients in the treatment group showed no statistical

significance, including the adverse events in the upper gastrointestinal tract or vascular constriction. According to the published data (Vandenbroucke *et al*., 2017), diphosphonate may have a high incidence rate of the adverse events in the upper gastrointestinal tract, which, however, was overridden by the evidence of randomized control trials that diphosphonate medication brings about little or no risk in the upper gastrointestinal tract. It has been reported (Tu *et al.,* 2018) that raloxifene-induced adverse events included the deep vein thrombosis, which was never shown in this study. In this study, in comparison with the single administration of risedronate sodium, co-administration of risedronate sodium and raloxifene ameliorated the hormone levels in serum, while some patients responded poorly to the single treatment, or even manifested a decline in BMD. Thus, co-administration with the anti-absorption drugs was taken into the consideration. Despite of the potential increase in BMD, it shows less significant efficacy in prophylaxis of fracture (Qi *et al.*, 2017). Other factors that should be taken into the consideration include the treatment-related benefit to organs other than bones and the risk factors of other diseases. Co-administration may augment the incidence rate, severity or types of adverse events. Most importantly, co-administration may produce an extremely high cost for some patients. Thus, patients should be informed of the benefit and risk of the anti-absorption treatment.

CONCLUSION

Overall, in treatment of PMOP, co-administration of risedronate sodium and raloxifene may benefit the patients more by increasing the BMD of lumber vertebrae and femoral neck, decreasing the bone transformation rate and ameliorating the VAS scores and hormone levels when comparing to the single administration of risedronate sodium.

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