Research Paper

Study on Application of Alfacalcidol Soft Capsule Combined with Raloxifene in the Postoperative Treatment of Postmenopausal Osteoporotic Thoracolumbar Fractures

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To discuss the effect of alfacalcidol soft capsule combined with raloxifene in the postoperative treatment of postmenopausal osteoporotic thoracolumbar fractures. Selected 94 patients with postmenopausal osteoporotic thoracolumbar fractures who underwent percutaneous vertebroplasty in our hospital from January 2019 to January 2021 and then randomly divided them into a control group and a combined group (n=47). After operation, control group received raloxifene tablets treatment, while combined group received alfacalcidol soft capsule and raloxifene tablets treatment. Both groups had no significant difference in scores of Oswestry disability index before drug therapy (p>0.05). After drug therapy, Oswestry disability index scores of both groups were lower than before therapy (p<0.05) and combined group had lower Oswestry disability index scores than control group (p<0.05). After drug therapy, the bone mineral density and bone mineral content of both groups were higher than before therapy (p<0.05) and these in combined group were higher than control group (p<0.05). After drug therapy, the levels of bone gla protein and bone alkaline phosphatase of both groups were higher than those before therapy (p<0.05), while the levels of beta-C-terminal telopeptide and type I procollagen N-terminal peptide of both groups were lower than before therapy (p<0.05) and the levels of bone gla protein and bone alkaline phosphatase in combined group were higher than control group (p<0.05) and the levels of beta-C-terminal telopeptide and type I procollagen N-terminal peptide in combined group were lower than control group (p<0.05). Both groups had no significant difference in adverse reactions rate (p>0.05). The fracture recurrence rate in combined group 1 y after operation was lower than control group (p<0.05). Application of alfacalcidol soft capsule combined with raloxifene in the postoperative treatment of postmenopausal osteoporotic thoracolumbar fractures can improve dysfunction and bone strength, and regulate bone metabolic indexes and reduce fractures recurrence rate with good safety.

Key words: Alfacalcidol soft capsule, raloxifene, menopause, osteoporotic, thoracolumbar fractures, bone strength, bone metabolism

Osteoporosis is a bone disease that occurs easily after 5-10 y of menopause in women. The main cause of the disease is abnormal bone cell function caused by the rapid decrease in estrogen content. Its main clinical manifestations include decreased Bone Mineral Density (BMD), bone damage and imbalance of bone metabolism, which are very easy to cause vertebral fracture[1,2]. Postmenopausal osteoporotic thoracolumbar fracture is one of the most serious complications of Postmenopausal Osteoporosis (POP), which seriously endangers the physical and mental health of postmenopausal women. Surgery is a conventional method for postmenopausal osteoporotic thoracolumbar fractures clinical treatment. Percutaneous Vertebroplasty (PVP) is one of the most widely used methods and anti-osteoporosis drugs are often used for adjuvant treatment[3], but the effect of basic treatment such as calcium tablets and vitamin D is poor. At present, raloxifene is commonly used clinically in the treatment of POP. As an effective estrogen regulator, it can selectively adjust bone metabolism indicators to achieve the purpose of inhibiting bone resorption

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and exert a good therapeutic effect on patients[4], but the curative effect when used alone is not ideal[5]. Gao *et al.*[6] found that alfacalcidol can promote bone formation, improve bone strength and play a positive role on osteoporosis. Therefore, this study specifically applied the combination of alfacalcidol and raloxifene to postmenopausal osteoporotic thoracolumbar fractures in the postoperative treatment, in order to improve the clinical treatment effect.

MATERIALS AND METHODS

Clinical data:

After approval by the hospital ethics committee, we selected 94 women patients with postmenopausal osteoporotic thoracolumbar fractures who underwent PVP in our hospital from January 2019 to January 2021 and then randomly divided them into a control group and a combined group (n=47). The ages in control group was from 54 to 73 y old, their average age is about (62.47±9.71) y old; the menopausal time was from 3 to 15 y, with an average of (5.09±1.01) y; the body mass index was from 16.63 to 26.81 kg/m^2, with an average of (21.52±4.07) kg/m^2; 21 people had thoracic spine fractures and 26 had lumbar spine fractures. The ages in combined group is from 55 to 75 y old, their average age is about (62.51±9.69) y old; the menopausal time is from 3 to 15 y, with an average of (5.11±1.04) y; the body mass index is from 16.56 to 26.89 kg/m^2, with an average of (21.49±4.06) kg/m^2; 23 people had thoracic spine fractures and 24 had lumbar spine fractures. Both groups had no statistical difference in general information ($p>0.05$).

Inclusion criteria: All women were naturally menopausal; all were in line with the "Expert Consensus on Diagnostic Criteria for Osteoporosis in China (2014 Edition)"[7] and all are primary fractures for the first time; all of them were single vertebral fracture of thoracolumbar spine and were treated with PVP surgery and no treatment for osteoporosis was received in the first 6 mo of this study.

Exclusion criteria: Fracture caused by secondary osteoporosis; severe organs, blood, mental diseases and other diseases; parathyroid dysfunction, diabetes and other metabolic diseases and allergies to the drugs used, drugs contraindications.

Method:

Patients in both groups were given basic treatment of calcium and vitamin D, Caltrate vitamin D calcium capsules (Sirio Pharma Co., Ltd., specification: 1 g/capsule, approval number: Guoshijianzi G201220445) were taken orally, twice a day, one capsule each time.

Control group: Besides receiving basic treatment, oral raloxifene tablets (Jiangsu Hengrui Medicine Co., Ltd., specification: 60 mg/tablet, approval number: Guoyaozhunzi H20050899), once a day, 1 tablet each time. The treatment time is 6 mo.

Combination group: Besides receiving the same treatment as control group, take alfacalcidol soft capsule (Nantong Huashan Pharmaceutical Co., Ltd., specification: 0.25 μg/capsule, approval number: Guoyaozhunzi H20000065), once a day, each time 2 capsules. The treatment time is 6 mo.

Observation indicators:

Compared the changes of thoracolumbar dysfunction before and after drug treatment of both groups: Adopted Oswestry Disability Index (ODI) scale[8] to score the patient's pain intensity, self-care ability in daily life, lifting, walking, sitting, standing, sleeping, social activities and each scores from 0 to 5 points. The higher the score, the more serious the dysfunction.

Compared the changes of thoracolumbar vertebral bone strength before and after drug treatment of both groups: Adopted dual-energy X-ray bone density meter to exam the BMD and Bone Mineral Content (BMC) of the patient's thoracolumbar spine (T9~L4). The BMD of the thoracolumbar vertebrae is taken as the average value of the measured vertebral BMD; the BMC of the thoracolumbar vertebrae is taken as the average value of the measured vertebral BMC.

Bone metabolism indexes were compared: Before and after drug treatment, 5 ml of the patient's forearm venous blood sample on an empty stomach was taken and centrifuged at 1200 r/min for 10 min, then radioimmunoassay was used to detect the levels of Bone Gla Protein (BGP), Bone Alkaline Phosphatase (BAP), Beta-C-Terminal Telopeptide (β-CTX) and Type I Procollagen N-Terminal Peptide (PINP).

Adverse reactions rate was compared: Common clinical adverse reactions of alfacalcidol soft capsules include nausea and vomiting, indigestion, dizziness, headache, skin rash, etc.; common clinical adverse reactions of raloxifene include dizziness, headache, skin rash, sweating, etc. Then calculate the adverse reactions rate in both groups.

Adverse reactions rate=number of adverse reactions/total number of patients×100 %.

Compared fracture recurrence of both groups: After drug therapy, conducted follow-up visits of the patients for a period of 1 y and recorded their fractures recurrence condition, and then calculated fractures recurrence rate.

Fractures recurrence rate=(number of reoccurring fractures/total number of patients)×100 %.

Statistical analysis:

Adopted Statistical Package for the Social Sciences (SPSS) 25.0 software for statistical analysis. Used mean±standard deviation ($\bar{x}\pm s$) to indicate measurement data and tested by t; the count data is described by Percent (%) and tested by χ^2. Any theoretical frequency >1 and <5 needs to be corrected for inspection and any theoretical frequency of 0 needs to use Fisher's exact inspection. $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Both groups had no significant difference in ODI scores before treatment ($p>0.05$). After treatment ODI scores were significantly lower than before therapy ($p<0.05$) and after treatment combined group had lower ODI scores than control group ($p<0.05$), as shown in Table 1.

Both groups had no significant difference in BMD and BMC before drug therapy ($p>0.05$). After treatment, BMD and BMC of both groups were higher than those before therapy ($p<0.05$) and combination group had higher BMD and BMC than control group ($p<0.05$), as shown in Table 2.

Both groups had no significant difference in BGP, BAP, CTX and PINP levels before drug therapy ($p>0.05$). After treatment, BGP and BAP levels of both groups were higher than those before therapy ($p<0.05$), β-CTX and PINP levels of both groups were lower than those before therapy ($p<0.05$) and combined group had higher BGP and BAP levels than control group ($p<0.05$), combined group had lower β-CTX and PINP levels than control group ($p<0.05$), as shown in Table 3.

Both groups had no statistical difference in adverse reactions rate ($p>0.05$), as shown in Table 4. During the 1 y follow-up, 4.26 % (2/47) fracture recurrence rate in combined group was significantly lower than 21.28 % (10/47) in control group. There is statistical difference between them ($\chi^2= 4.681$, $p=0.030$).

TABLE 1: CHANGES IN ODI SCORES BEFORE AND AFTER DRUG THERAPY ($\bar{x}\pm s$; POINTS)

Group	n	Group n		t	p
		Before treatment	After treatment		
Combined group	47	32.91±6.02	13.84±2.31	20.276	<0.001
Control group	47	32.85±6.05	18.72±3.39	13.968	<0.001
t		0.048	8.155		
p		0.962	<0.001		

TABLE 2: CHANGES IN BONE STRENGTH BEFORE AND AFTER DRUG THERAPY ($\bar{x}\pm s$)

Group	n	BMD (g/cm^3)		t	p	BMC (g/cm)		t	p
		Before treatment	After treatment			Before treatment	After treatment		
Combined group	47	0.65±0.11	0.85±0.16	7.062	<0.001	0.72±0.12	0.87±0.16	5.353	<0.001
Control group	47	0.66±0.10	0.74±0.13	3.344	0.001	0.73±0.14	0.81±0.12	2.974	0.004
t		0.461	3.658			0.372	2.057		
p		0.646	<0.001			0.711	0.043		

TABLE 3: CHANGES IN BONE METABOLISM INDEXES (x̄±s)

Group	n	Time	BGP (μg/l)	BAP (μg/l)	β-CTX (ng/ml)	PINP (ng/ml)
Combined group	47	Before treatment	6.85±1.09	12.47±2.23	0.81±0.15	63.26±5.81
		After treatment	10.43±2.02①②	19.79±3.62①②	0.62±0.13①②	51.42±4.49①②
Control group	47	Before treatment	6.82±1.07	12.53±2.28	0.82±0.16	63.31±5.84
		After treatment	8.97±1.66①	16.34±3.11①	0.69±0.14①	57.38±4.92①

Note: ①Compared with the situation before treatment, p<0.05; ②compared with control group, p<0.05; BGP: Bone Gla Protein; BAP: Bone Alkaline Phosphatase; β-CTX: Beta-C-Terminal Telopeptide and PINP: Type I Procollagen N-Terminal Peptide

TABLE 4: COMPARISON OF ADVERSE REACTIONS (CASES; %)

Group	n	Nausea and vomiting	Dizziness and headache	Skin rash	Dyspepsia	Total incidence of adverse reactions
Combined group	47	2 (4.26)	1 (2.13)	2 (4.26)	0 (0.00)	5 (10.64)
Control group	47	2 (4.26)	0 (0.00)	1 (2.13)	1 (2.13)	4 (8.51)
χ^2		0.261	—	0.000	—	0.000
p		0.609	1.000	1.000	1.000	1.000

POP is a common primary osteoporosis and thoracolumbar fracture is one of its common complications[9]. It is very necessary for postmenopausal patients with osteoporotic thoracolumbar fractures to receive postoperative drug treatment. The adjuvant treatment with anti-osteoporosis drugs can restore bone turnover, improve BMD, promote the recovery of vertebral bone function and achieve ideal therapeutic effect. Raloxifene can replace estrogen to significantly improve bone turnover rate, protect bone and has good safety. It can be used as a postoperative therapeutic drug for postmenopausal osteoporotic thoracolumbar fractures[10].

Alfacalcidol can promote bone mineralization, strengthen calcium absorption and reduce osteolysis. It can also be used for postoperative treatment of postmenopausal osteoporotic thoracolumbar fractures[11]. However, the efficacy of the above two drugs when used alone is not ideal. Therefore, how to achieve a better effect on postmenopausal osteoporotic thoracolumbar fractures postoperative treatment is still a problem worthy of in-depth discussion.

This study found that after drug therapy combination group had obviously lower ODI scores than control group and it had significantly higher BMD, BMC, BGP and BAP levels than control group and it had significantly lower β-CTX and PINP levels than control group. It shows that the combined treatment of alfacalcidol and raloxifene can significantly improve the postoperative somatic dysfunction of postmenopausal patients with osteoporotic thoracolumbar fractures, significantly improve bone strength, improve bone metabolism and play a better effect than raloxifene alone. The reason is that raloxifene is a selective estrogen regulator. It replaces estrogen and binds to receptor, activates estrogen receptor, opens estrogen pathway, regulates bone transformation index to normal level, inhibits bone absorption and maintains the stability of bone microenvironment, thus showing a good therapeutic effect[12]. Alfacalcidol can increase the content of 1,25-dihydroxyvitamin D3 in blood circulation and the absorption rate of calcium and phosphate in intestine, so as to increase the content of calcium in blood, deposit in bones under the action of vitamin D and promote bone formation. At the same time, alfacalcidol can also reduce the level of parathyroid hormone in the internal environment, reduce osteolysis, promote the recovery of osteocalcin, accelerate bone formation and enhance bone strength and have a good therapeutic effect[13]. Alfacalcidol combined with raloxifene can play a synergistic role, reduce bone resorption, improve bone formation and significantly improve the therapeutic effect on POP[14]. This result is consistent with that reported by Xiong *et al.*[15] that the therapeutic effect of alfacalcidol combined with raloxifene on POP is better than that of raloxifene alone.

The results of this study showed that both groups were similar in total adverse reactions rate, indicating that the combined treatment of alfacalcidol soft capsules and raloxifene will not cause obvious adverse reactions to patients and has good safety. This study found that combination group had significantly lower fracture recurrence rate than control group during follow-up, indicating that the application of alfacalcidol soft capsule combined with raloxifene in the postoperative treatment of postmenopausal osteoporotic thoracolumbar fractures can significantly reduce the fracture recurrence rate and the effect is more lasting. Nan[16] found that bone density is one of the main factors affecting patients' re-fractures after surgery and increased bone density can effectively reduce the incidence of re-fractures. In this study, the combination of alfacalcidol capsules and raloxifene can significantly increase the BMD of postmenopausal patients with osteoporotic thoracolumbar fractures, so it can effectively prevent the recurrence of fractures.

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In summary, alfacalcidol soft capsules combined with raloxifene can significantly improve the patient's dysfunction, increase bone strength and promote the recovery of bone metabolic indexes when used in postmenopausal osteoporotic thoracolumbar fractures. It has a good therapeutic effect on POP. In addition, it has good safety and can significantly reduce the recurrence rate of fractures. It is worthy to be popularized in the postoperative treatment of postmenopausal osteoporotic fractures.

Author's contribution:

Yun Xiang and Chuancheng Feng have contirbuted equally to this work

Conflicts of interest:

The authors declared no conflicts of interest.

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