

Original Research Article

Efficacy of the combination of Tenghuangjiangu tablets, alfacalcidol capsules and caltrate D3 tablets in osteoporotic vertebral compression fracture, and their effects on bone metabolic indices

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Abstract

Purpose: To investigate the efficacy of the combination of Tenghuangjiangu tablets, Alfacalcidol capsules and Caltrate D3 tablets in osteoporotic vertebral compression fracture (OVCF) and their effects on bone metabolic indices.

Methods: Ninety-six patients with OVCF were randomly categorized into study group (SG) and control group (CG). Patients in the CG orally took Caltrate D3 tablets, while those in the SG were given Tenghuangjiangu tablets and Alfacalcidol capsules in addition to caltrate D3 tablets. The Bone mineral density (BMD) values and the treatment efficacy were compared. The levels of bone metabolism markers (PINP, β -CTX, BGP, NBAP), CT and PTH were determined using electrochemiluminescence immunoassay, while Ca^{2+} levels were assessed using liquid level detection. The incidence of adverse reactions (re-fracture, gastrointestinal reaction, hypotension and abnormal coagulation function) were compared.

Results: Treatment efficacy in the SG was 91.67 %, which was significantly higher than that in the CG (81.25 %; $p < 0.05$). Before treatment, the two groups showed no significant differences in BMD, PINP, β -CTX, BGP, NBAP, Ca^{2+} , CT, and PTH levels ($p > 0.05$). After treatment, the SG exhibited significantly higher BMD, PINP, BGP, NBAP, Ca^{2+} and CT levels, and showed lower β -CTX and PTH levels than the CG ($p < 0.05$). The SG exhibited a significantly lower incidence rate of adverse reactions than that the CG ($p < 0.05$).

Conclusion: The combination of Tenghuangjiangu tablets, Alfacalcidol capsules, and Caltrate D3 tablets, improves bone metabolic indices, bone density and treatment efficacy while reducing the incidence rate of adverse reactions.

Keywords: Tenghuangjiangu tablets, Alfacalcidol, Caltrate D3 tablets, Osteoporotic spine fracture

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INTRODUCTION

Osteoporosis is a systemic disease, and its incidence is increasing year by year. It is

characterized by reduced bone mass, increased brittleness of bones, and pathological fractures which can occur with minor external forces, especially in the spine [1,2]. Studies have

pointed out that patients with osteoporosis are at a greatly increased risk of delayed healing of fractures, non-healing or even re-fracture after spine fracture surgery due to imbalance between bone resorption and bone formation *in vivo*, and disturbance of bone metabolism [3,4].

Osteoporosis is a common orthopedic disorder that occurs mostly in middle-aged and elderly people, and is characterized by reduced bone density, decreased bone content, and severe destruction of bone tissue [5]. Middle-aged and elderly people are more susceptible to fractures, among which osteoporotic vertebral compression fractures (OVCF) are the most common type, mainly manifested as pain, spinal deformation and osteonecrotic deformity, which seriously reduces the quality of life of patients [6]. With the development of minimally invasive techniques, percutaneous kyphoplasty has become the first choice for patients with OVCF, and has achieved satisfactory results. The current postoperative treatments involve calcium supplementation, promotion of bone formation and antagonism of bone resorption. The effects however are not ideal [7,8].

Tenghuangjiangu tablet, is a herbal compound possessing analgesic and blood-activating properties, and is applied for a variety of spinal disorders. Alfacalcidol, an osteotriol analogue inhibits parathyroid hormone synthesis as well as bone resorption, promotes matrix and collagen synthesis, and alleviates osteoporosis [9]. Some studies have shown that the combination of Tenghuangjiangu tablets, Alfacalcidol capsules and calcium supplements can improve the therapeutic effect of patients with spinal fractures [10]. Therefore, this study reports the effect of the combination of Tenghuangjiangu tablets, Alfacalcidol capsules, and Caltrate D3 tablets on the efficacy and bone metabolic indices of patients with osteoporotic spinal fractures.

METHODS

General patient profile

Ninety-six patients with OVCF who were admitted to the Shenzhen People's Hospital from June 2015 to June 2018 were registered for the study. This study was approved by the Ethics

Committee of Shenzhen People's Hospital, and followed the ethical principles of the Declaration of Helsinki for medical research involving human subjects [12]. All patients voluntarily participated in the study and signed consent forms.

Inclusion criteria

Patients who were clinically diagnosed with OVCF and treated with percutaneous kyphoplasty after surgery, who had bone density of < 2.5, as well as complete clinical and imaging data, were included [11].

Exclusion criteria

Those with other sports joint system diseases, combined with those with malignant tumors and severe cardiac insufficiency, in addition to those who had allergy to the drugs used in the research were excluded. The patients were randomized to study group (SG, n = 48) and control group (CG, n = 48). Both groups exhibited no statistical differences in gender, age, disease duration, fracture site and gradation ($p > 0.05$) (Table 1).

Treatments

All patients received orthopedic routine care, and were given unified functional exercise and dietary management. The CG was given Caltrate D3 tablets (H10950029, 600 mg × 60 s, Jiangsu Wyeth Pharmaceutical Co., Ltd.), 1 tablet/time, twice daily. The SG was given Tenghuangjiangu tablets (Z20090570, 0.5 g × 24 s, Hunan Fangsheng Pharmaceutical Co., Ltd.), 3 tablets/time, twice daily, and Alfacalcidol capsules (J20130162, 0.25 µg × 10 s × 2 plates/box, Teva Pharmaceutical Industries Ltd. Ltd. distribution), 2 capsules/time, 1 time/day in addition to caltrate D3 tablets. All medications were administered after meals.

Evaluation of outcomes

Treatment efficacy

The treatment efficacy of patients in both groups was assessed after 2 months of continuous treatment.

Table 1: Comparison of baseline data (n = 48)

Group	Age (years)	Sex (male/female)	Duration of disease (Year)	Fracture site (thoracic/ lumbar spine)	Fracture grading (I/II/III)
Control	55.39±4.04	25/23	1.23±1.01	13/35	12/23/13
Study	56.14±4.05	24/24	1.28±1.03	16/32	11/22/15

The efficacy assessment of spinal fracture was based on four levels [13,14]. *Cured*: clinical symptoms and signs disappeared, bone density was normal, and the fracture line was blurred; *Markedly effective*: symptoms and signs were improved significantly, bone density decreased mildly, and a large amount of bone scabs grew at the fracture; *Effective*: symptoms and signs were improved basically, bone density decreased moderately, and a medium amount of bone scabs grew at the fracture; *Ineffective*: symptoms and signs did not improve, moderate decrease in bone density, with moderate amount of bone scab growth at the fracture site. The effective rate (E) was calculated using Eq 1.

$$E = \{(C+ME+EC)/T\}100 \dots\dots\dots (1)$$

where C = cured cases, ME = markedly effective cases, EC = effective cases and T = total number of cases.

Bone mineral density (BMD)

The BMD values at various sites were measured. Bone density was performed by dual-energy X-ray bone densitometer (Xi'an Baide Instrument and Equipment Co., Ltd., Model EXA-3000, Xi'an, China), and the measurement sites were T6 ~ T8 of the thoracic spine, L1 ~ L3 of the lumbar spine, greater trochanter and Ward triangle.

Levels of bone metabolism marker and electrolyte biochemical indices

Type I collagen N-terminal pro-peptide (PINP), β -collagen degradation product (β -CTX), serum osteocalcin (BGP), bone alkaline phosphatase (NBAP), calcitonin (CT) and parathyroid hormone (PTH) levels were measured by electrochemiluminescence immunoassay, using a fully automated chemiluminescence immunoassay analyzer (Beijing Plantronics Co., Ltd., Model PHX-2014, Beijing, China). Calcium (Ca^{2+}) was determined by liquid level detection technique, using a fully automatic blood gas electrolyte analyzer (M397158) from Beijing Xihua Yi Technology Co. (Beijing, China). All the test kits were provided by the corresponding companies, and the operational procedures were performed strictly in line with the manufacturer

instructions, which were completed by the Laboratory Department of Shenzhen People's Hospital.

Assessment of incidence of adverse reactions

The incidence of adverse reactions (I) such as re-fracture, gastrointestinal reaction, hypotension and abnormal coagulation function was analyzed using Eq 2.

$$I = (\sum nR/T)100 \dots\dots\dots (2)$$

where $\sum nR$ = the sum of the number of adverse reactions.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) 23.0 (IBM, Armonk, USA) was utilized to analyze the data. The χ^2 test was applied for count data. The t-test was applied for measurement of data, which are described as, mean \pm standard deviation (SD). A significance level of $\alpha = 0.05$ was set.

RESULTS

Comparison of general profile

Both groups exhibited no statistical differences in the aspect of age, sex (male/female), duration of disease, fracture site (thoracic/lumbar), and fracture grading (I/II/III) ($p > 0.05$, Table 1).

Treatment efficacy

Treatment efficacy in the SG was 91.67 %, significantly higher than 81.25 % in the CG ($p < 0.05$, Table 2).

BMD values at various sites

Both groups exhibited no significant differences in the BMD values of T6 - T8, L1 - L3, major trochanter, and Ward's triangle before treatment ($p > 0.05$). The SG exhibited significantly higher BMD values of T6 - T8, L1 - L3, greater trochanter, and Ward's triangle than the CG after treatment ($p < 0.05$, Table 3).

Table 2: Comparison of the efficacy of patients {n (%); n = 48}

Group	Cured	Markedly Effective	Effective	Ineffective	Effective rate (%)
Study	4 (8.33)	24 (50.00)	16 (33.33)	4 (8.33)	44(91.67) ^a
Control	2 (4.17)	22 (45.83)	15 (31.25)	9 (18.75)	39 (81.25)

Note: ^a $p < 0.05$ vs. control group

Table 3: Comparison of BMD values at various sites (mean ± SD; n = 48)

Time	Group	T6~T8 (g/cm ³)	L1~L3 (g/cm ³)	Big rumble (g/cm ³)	Greater trochanter (g/cm ³)
Before treatment	Control	0.71±0.12	0.75±0.08	0.65±0.13	0.59±0.10
	Study	0.72±0.09	0.75±0.09	0.66±0.11	0.60±0.11
After treatment	Control	0.78±0.08 ^b	0.81±0.18 ^b	0.71±0.12 ^b	0.67±0.08 ^b
	Study	0.87±0.12 ^{ab}	0.89±0.07 ^{ab}	0.80±0.10 ^{ab}	0.74±0.07 ^{ab}

^a*p* < 0.05 vs. control group; ^b*p* < 0.05 vs. before treatment

Levels of bone metabolic indices

Both groups exhibited no significant difference in the levels of PINP, β-CTX, BGP and NBAP before treatment (*p* > 0.05). After treatment, both groups showed higher levels of PINP, BGP and NBAP, and lower levels of β-CTX than before treatment (*p* < 0.05). The SG exhibited higher levels of PINP, BGP and NBAP, and exhibited lower levels of β-CTX than the CG (*p* < 0.05, Figure 1).

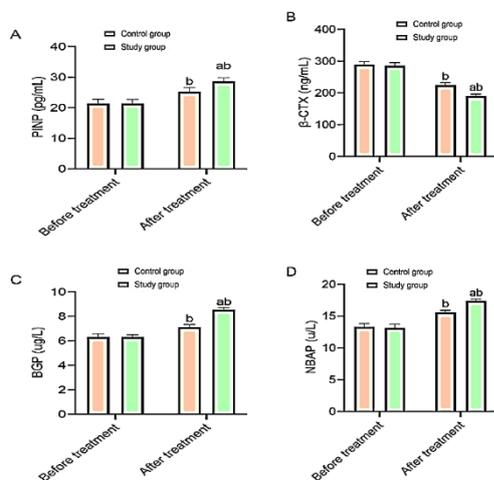


Figure 1: Effect of the combination use of Tenghuangjiangu tablets, Alfacalcidol capsules, and Calcium D3 tablets on bone metabolic indices in patients with OVCF. The SG exhibited significantly higher levels of PINP (A), BGP (C), and NBAP (D), and exhibited significantly lower level of β-CTX (B) than the CG. Note: ^a*p* < 0.05 vs. control group; ^b*p* < 0.05 vs. before treatment

Electrolyte biochemical indices

Both groups exhibited no significant differences in Ca²⁺, CT and PTH levels before treatment (*p* > 0.05). After treatment, the SG exhibited higher Ca²⁺ and CT levels, and lower PTH levels than the CG (*p* < 0.05, Figure 2).

Levels of inflammatory indices

Both groups exhibited no significant differences in the IL-2, IL-6 and TNF-α levels before treatment (*p* > 0.05). After treatment, the SG

exhibited lower levels of IL-2, IL-6 and TNF-α than the CG (*p* < 0.05, Figure 3).

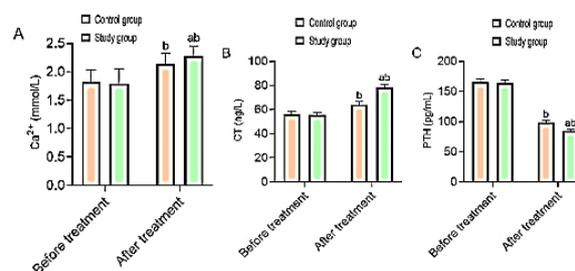


Figure 2: Effects of the combination of Tenghuangjiangu tablets, Alfacalcidol capsules, and Calcium D3 tablets on the biochemical indices of electrolytes in patients with OVCF. The SG exhibited higher Ca²⁺ (A) and CT (B) levels and lower PTH (C) levels than the CG. Note: ^a*p* < 0.05 vs. control group; ^b*p* < 0.05 vs. before treatment

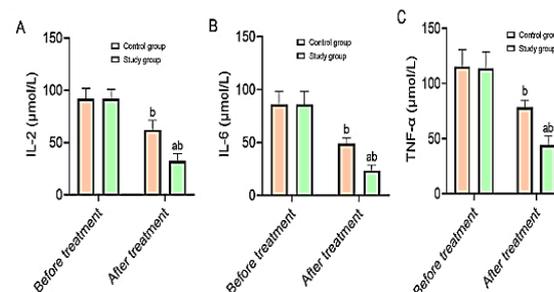


Figure 3: Effect of the combination of Tenghuangjiangu tablets, Alfacalcidol capsules, and Calcium D3 tablets on inflammatory factors in patients with OVCF. The SG exhibited significantly lower levels of IL-2 (A), IL-6 (B), and TNF-α (C) than the CG. Note: ^a*p* < 0.05 vs. control group; ^b*p* < 0.05 vs. before treatment

The occurrence of adverse reactions

Two cases of re-fracture, two cases of gastrointestinal reaction, two cases of hypotension and one case of coagulation function occurred in the CG, and the rate of adverse reactions was 14.58 %. One case of re-fracture, two cases of gastrointestinal reaction and one case of hypotension occurred in SG, and the incidence rate was 8.33 % (*p* < 0.05, Table 4).

Table 4: Comparison of adverse reactions (n (%), n = 48)

Group	Re-fracture	Gastrointestinal reaction	Hypotension	Coagulation abnormalities	Total incidence rate (%)
Control	2 (4.17)	2 (4.17)	2 (4.17)	1 (2.08)	7(14.58) ^a
Study	1 (2.08)	2 (4.17)	1 (2.08)	0 (0.00)	4 (8.33)

^aP < 0.05 vs. control group

DISCUSSION

The regulation of the bone metabolic process and the improvement of osteoporosis after surgery is the primary challenge in the management of patients with OVCF. Traditional drugs such as calcium and phosphorus supplements can no longer meet the clinical requirements for efficacy. Tenghuangjiangu tablets and alfacalcidol capsules are effective in the treatment of fractures, and their combined application with calcium supplementation drugs e.g., Caltrate D3 tablets in patients with OVCF is attracting significant attention in clinical research [15].

Traditional Chinese medicine has been applied in fractures dating back into historical times. It is believed that the tendons and veins are damaged after the fracture of the limbs, so that blood flow in the veins does not run smoothly, resulting in stasis and swelling of the limbs, and that activating blood circulation and removing stasis can make the qi and blood flow smoothly. Tenghuangjiangu tablets are prescribed by the famous Chinese medicine practitioner Professor Liu Bo-ling according to the theory of "tonifying the kidney to cure bone", which has the effect of tonifying the kidney, relieving pain and invigorating the blood [16]. Alfacalcidol capsules are a potent vitamin D derivative that effectively relieves skeletal and muscle pains, and improves osteoporosis. It works by promoting the synthesis of its growth factors, collagen and bone matrix; improving the microenvironment of bone cells, and facilitating the repair of cartilage tissue; increasing the 1, 25-dihydroxyvitamin D3 level and promoting small intestine absorption of calcium, reducing PTH levels, and promoting bone formation. Other actions include, regulating muscle metabolic processes and innervation of muscles, enhancing cellular contractility, and reducing the risk of re-fracture [17]. Caltrate D3 tablets, as a vitamin D and calcium carbonate compound, not only have high calcium content, but also promote the absorption of calcium ions and the metabolism of phosphorus [18].

In this study, the efficacy of the combination therapy was 91.67 % in the SG and 81.25 % in the CG, indicating that the combined use of Tenghuangjiangu tablets, Alfacalcidol capsules, and Caltrate D3 tablets improved the BMD of

OVCF patients and promoted the growth and healing of fracture line, thereby demonstrating better efficacy. The BMD is a key index representing bone strength and can accurately predict osteoporotic spine fracture, with the lower BMD indicating the greater risk of fracture, and the BMD values vary in different parts of the body, so a comprehensive evaluation of the bone health of each part is of great significance to the prevention of fracture [19]. In this research, the BMD values of T6~T8, L1~L3, greater trochanter and Ward's triangle were significantly higher in the SG than in the CG, indicating that the combination of Tenghuangjiangu tablets, Alfacalcidol capsules and Caltrate D3 tablets can promote the conversion of minerals into bones by promoting blood circulation, increasing calcium and phosphorus absorption and regulating kidney function, thus increasing the bone content and improving the efficacy against osteoporosis. The findings of Liu and Lu [20] indicated that the combination of Tenghuangjiangu tablets and Alfacalcidol capsules could effectively increase BMD and reduce fracture risk in the elderly with osteoporosis, which is consistent with this study.

The morphological changes of bone depend on the changes in the activity of osteoblasts and osteoclasts, and the processes of bone resorption and bone formation are always in a dynamic equilibrium. Osteoporosis and fracture are both caused by the imbalance of the two kinds of cell functional activities. When the bone turnover changes, the level of bone metabolism alters, which can be reflected in time by bone metabolism markers [21]. The PINP, as the only collagen product translated and synthesized by osteoblast type I pre-collagen peptide *in vivo*, reflects the activity of osteoblasts, the rate of type I collagen synthesis and the state of bone formation. It is not related to age and gender, and is a specific indicator of bone formation. The β -CTX is a peptide fragment containing specific epitopes, which can be further decomposed by PINP. The BGP is a protein rich in γ -carboxyglutamic acid, mainly synthesized and released by newborn osteoblasts, most of which are mineralized and deposited in the bone matrix, and it is almost not affected by osteoclast metabolism, and more accurately and sensitively reflects the activity level of osteoblasts. The NBAP is a phenotypic marker enzyme, mainly expressed in osteoblasts, and this enzyme is

secreted in large quantities to promote bone mineralization when calcium levels are reduced and calcium salt deposition is insufficient, which is the best indicator of bone formation process [22,23].

In this study, the SG had higher levels of PINP, BGP, and NBAP, and lower levels of β -CTX than the CG, indicating that the combination of Tenghuangjiangu tablets, Alfacalcidol capsules and Caltrate D3 tablets can increase osteoblast activity, promote the process of mineral-to-bone conversion, improve bone metabolism, improve osteoporosis, and ultimately accelerate fracture healing. Jiao *et al* found that Alfacalcidol capsules and blood-stasis activating remedies can promote post-fracture osteogenesis and shorten the time to fracture healing [24], which is similar to the results of this research. Ca^{2+} is the key cation for improving osteoporosis, and data shows that most osteoporotic patients have very low calcium levels, and calcium supplementation is used throughout the treatment of osteoporotic patients; The CT is an endogenous hormone that regulates calcium metabolism, inhibits osteoclast activity, promotes calcium transfer to bone, and accelerates bone scab growth and fracture recovery. When calcium and phosphorus metabolism are imbalanced, parathyroid function is hyperactive, PTH secretion is increased, osteoclast and osteoblast activities are enhanced, and bone metabolism is in a state of high conversion, which delays fracture healing and increases fracture risk [25].

The study group had higher Ca^{2+} and CT levels and lower PTH levels than the CG, indicating that the combination of Tenghuangjiangu tablets, Alfacalcidol capsules and Caltrate D3 tablets could increase blood calcium levels, promote bone formation and healing, and reduce the risk of re-fracture in OVCF patients. In addition, the SG had an incidence of adverse reactions of 8.33 %, lower than 14.58 % in the CG, indicating that Tenghuangjiangu tablets, Alfacalcidol capsules and Caltrate D3 tablets could reduce the risk of postoperative adverse reactions in OVCF patients, and improve the effects of the treatment. The research of Huang *et al* showed that Tenghuangjiangu tables and Alfacalcidol capsules supplemented with calcium were more effective and had lower rates of adverse reactions in patients with spinal fractures [26], which is consistent with this study.

CONCLUSION

The combination of the three drugs results in improvement of blood circulation, and reduce pain and swelling on the one hand, but then

enhance osteoblast activity, improve bone metabolism, and promote bone formation on the other hand. Thus, it can potentially improve osteoporosis, promote fracture healing, and reduce occurrence of adverse reactions.

DECLARATIONS

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Ethical approval

This study was approved by the Ethics Committee of Shenzhen People's Hospital in China.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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