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Original Article

Effects of Combined Application of Percutaneous Vertebroplasty and Zoledronic Acid on Bone Mineral Density, Bone Metabolism, NPY and PGE2 in Elderly Patients with Osteoporotic Lumbar Vertebral Compression Fracture

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Abstract

Objective: To investigate the effects of the combined application of percutaneous vertebroplasty and zoledronic acid on bone mineral density (BMD), bone metabolism, neuropeptide Y (NPY) and prostaglandin E2 (PGE2) in elderly patients with osteoporotic lumbar vertebral compression fracture (OVCF). **Methods**: The medical records of 118 elderly patients with OVCF who received treatment at our hospital from March 2018 to March 2020 were collected and analyzed retrospectively. Vertebral body height, spinal function, pain degree, and lumbar BMD were compared between the two groups upon admission and three years after the operation. Additionally, the levels of bone-specific alkaline phosphatase (BALP), 25-hydroxyvitamin D (25-(OH)D), beta collagen degradation fragments (β-CTx), neuropeptide Y (NPY), and prostaglandin E2 (PGE2) in the two groups were measured at admission and three years after the operation. Furthermore, complications in the two groups within three years after the operation were documented. **Results**: After three years post-operation, the combination group showed a significantly greater improvement in vertebral body height compared to the control group ($P<0.05$). Moreover, the combination group exhibited a significantly lower Oswestry Disability Index (ODI) score compared to the control group ($P<0.05$). **Conclusion**: In elderly patients with OVCF, the combined use of zoledronic acid and percutaneous vertebroplasty is effective in improving lumbar function, BMD, and bone metabolism indices, while reducing pain and the levels of NPY and PGE2.

Keywords: Bone Metabolism, Osteoporotic Lumbar Vertebral Compression Fracture, Percutaneous Vertebroplasty, Zoledronic Acid

Introduction

Osteoporosis is commonly diagnosed among the elderly, especially in women[1]. Osteoporotic vertebral compression fracture is a frequently encountered type of fracture in clinical practice, particularly in the elderly population[2]. As age increases, there is a gradual decrease in bone mineral density (BMD), leading to increased bone fragility and a higher susceptibility to fractures[3]. European research data indicate an annual prevalence rate of 12.1/1000 for osteoporotic vertebral compression fractures, with the rate among males being 6.8/1000[4]. Common symptoms of osteoporotic lumbar vertebral compression fracture (OVCF) include low back pain, abnormal spinal curvature, loss of stature, and difficulty in walking[5]. Multiple studies have suggested that individuals over the age of 65 with vertebral compression fractures have a higher mortality rate compared to a control group, and this risk tends to increase with the number of fractures[6].

Conservative treatments for senile osteoporotic lumbar fractures include bed rest, anti-osteoporosis drugs, painkillers, physical therapy, and wearing braces, which can provide some relief during the fracture healing process[7].

The authors have no conflict of interest.

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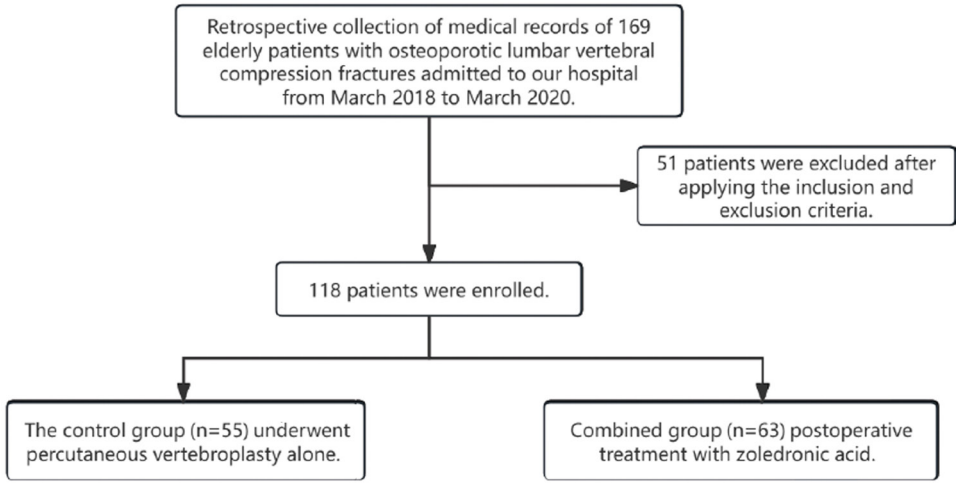

Figure 1. Study Flow chart.

However, these conservative treatments often require an extended duration for symptom relief. In some cases, they may not fully restore the normal shape of the spine and can lead to complications such as sacrococcygeal region pressure sores and venous thrombosis of the lower limbs[8].

Nowadays, percutaneous vertebroplasty has become the most commonly used treatment method for senile osteoporotic lumbar fractures. This interventional surgery is employed to quickly relieve pain and achieve vertebral stability. With the advantages of simplicity in operation and minimal trauma, it swiftly alleviates pain by injecting bone cement into the patient's vertebral body with the assistance of the imaging system[9]. However, surgical treatment alone cannot guarantee the absence of recurrence for patients with osteoporosis. Therefore, incorporating drug treatment is necessary to concurrently improve the bone mineral density (BMD) of patients. Bisphosphonate, commonly used in treating various bone diseases and calcium metabolic diseases, can specifically combine with hydroxyapatite in bone, inhibiting osteoclast activity, thus inhibiting bone resorption, increasing bone density, and reducing the risk of osteoporotic fracture[10]. Zoledronic acid, a third-generation nitrogen-containing bisphosphonate, similarly reduces bone resorption by inhibiting the activity of bone resorption cells[11]. However, in comparison with traditional bisphosphonate drugs, zoledronic acid is considered a more potent bone resorption inhibitor, and its inhibitory effect is more enduring[12].

This study aimed to assess the clinical effectiveness of combining percutaneous vertebroplasty with zoledronic acid in the therapy of elderly patients with OVCF and to clarify the effect on patients by comparing those who received zoledronic acid with those who did not.

Materials and Methods

During the study period, 169 elderly patients with osteoporotic lumbar vertebral compression fractures were admitted to our hospital. After applying exclusion and inclusion criteria, 118 patients were included in the final analysis. Their medical records, covering the period from March 2018 to March 2020, were collected and analyzed retrospectively. Among them, 55 patients who underwent percutaneous vertebroplasty alone were assigned to the control group, while 63 patients who received both percutaneous vertebroplasty and zoledronic acid were assigned to the combination group.

Inclusion and Exclusion Criteria

Inclusion Criteria

- Patients diagnosed with osteoporosis.
- Patients diagnosed with lumbar vertebral compression fracture through imaging.
- Patients with a simple vertebral compression fracture who have not received conservative treatment.
- Patients aged 60 years and above.
- Patients who have undergone percutaneous vertebroplasty.
- Patients with detailed medical records and follow-up data.

Exclusion Criteria

- Patients with comorbid spinal tumor or burst vertebral fracture.
- Patients with a history of spinal surgery.
- Patients with severe spinal deformity.
- Patients who are allergic to therapeutic drugs.

The study flow is shown in Figure 1.

Table 1. Baseline data.

		Control group (n=55)	Combination group (n=63)	t/χ^2	P
Age (years)		68.98±4.74	68.62±4.29	0.433	0.666
Sex	Male	16 (29.09)	14 (22.22)	0.731	0.393
	Female	39 (70.91)	49 (77.78)		
BMI	<28 kg/m^2	23 (41.82)	23 (36.51)	0.348	0.555
	≥28 kg/m^2	32 (58.18)	40 (63.49)		
ASA classification	Class I	31 (56.36)	40 (63.49)	0.623	0.430
	Class II	24 (43.64)	23 (36.51)		
Number of vertebral fractures	One	6 (10.91)	10 (15.87)	1.050	0.789
	Two	19 (34.55)	18 (28.57)		
	Three	22 (40.00)	24 (38.10)		
	Four	8 (14.54)	11 (17.46)		
Course of osteoporosis	≤1 years	24 (43.64)	21 (33.33)	1.321	0.250
	>1 years	31 (56.36)	42 (66.67)		
Injection amount of bone cement (mL)		4.19±1.36	4.06±1.11	0.572	0.569
Injection mode of bone cement	Unilateral	41 (74.55)	51 (80.95)	0.702	0.402
	Bilateral	14 (25.45)	12 (19.05)		

Therapeutic regimen

The control group underwent treatment with percutaneous vertebroplasty. The procedure involved placing the patient in a prone position after local anesthesia. Fluoroscopy, utilizing a mobile C-arm X-ray machine (Siemens Shanghai MEDICAL Equipment Ltd., model: Cios Select), was employed to precisely locate the focal point. Subsequently, unilateral or bilateral punctures outside the pedicles were made to establish a working channel. A self-setting calcium phosphate bone cement was uniformly stirred. Once the cement reached a paste-like consistency, 2.5-5.0 ml of bone cement was gradually injected into each vertebral body through the puncture needle. Continuous fluoroscopy via a C-arm was used to observe the filling and leakage of the bone cement during the injection. After injection, the needle core was inserted into the needle sleeve, and the bone cement was gradually delivered into the vertebral body. Post-operation, the puncture channel was removed, and pressure was applied for dressing. Patients were allowed to mobilize with the assistance of protective gear 48 hours after the operation and were encouraged to engage in functional exercises one week after the procedure. The exercise regimen primarily focused on active exercises, with passive exercises serving as a supplementary component.

Based on the treatment applied to the control group, the combination group received 5mg of zoledronic acid (Yangzijiang Pharmaceutical Group Sichuan Hairong Pharmaceutical Co., Ltd.) along with a 250mL infusion of 0.9% sodium chloride through intravenous drip for a minimum of 15 minutes on the third day after the operation. Following intravenous infusion, the infusion tube was rinsed with 0.9% sodium chloride. This injection was administered annually over a three-year period. Patients receiving zoledronic acid may experience post-medication symptoms. As part of the treatment protocol, acetaminophen extended-release tablets were administered for antipyretic and analgesic relief at a prescribed dosage of 650mg, twice a day. Additionally, patients were given 20mg of metoclopramide and 40mg of pantoprazole once a day to prevent gastrointestinal reactions.

Outcome Measures

1. The vertebral body height of each patient was measured and recorded at admission and three years after the operation.
2. The Oswestry Disability Index (ODI) was utilized to evaluate the spinal function of both groups at admission and three years post-operation. A lower ODI score indicates better spinal function.
3. The Visual Analogue Scale (VAS) was employed to assess the pain level experienced by patients at admission and three years post-operation. VAS is a 10-point scale, with higher scores indicating a greater degree of pain.
4. The Bone Mineral Density (BMD) of patients' lumbar spine was measured using a dual-energy X-ray detector (model: SGY-II) at admission and three years post-operation.
5. Bone metabolism markers, including bone-specific alkaline phosphatase (BALP), 25-hydroxyvitamin D (25-(OH)D),

Table 2. Comparison of vertebral body height and vertebral function.

	Vertebral body height (cm)		ODI score	
	Before surgery	Three years after surgery	Before surgery	Three years after surgery
Control group (n=55)	11.32±1.45	20.05±11.99	37.35±3.51	28.44±2.50
Combination group (n=63)	11.52±1.43	23.3±12.39	36.91±2.83	23.67±2.84
t	0.753	7.959	0.753	9.619
P	0.453	<0.001	0.453	<0.001

Table 3. Comparison of pain score and bone mineral density.

	VAS score		Bone mineral density (cm^2/g)	
	Before surgery	Three years after surgery	Before surgery	Three years after surgery
Control group (n=55)	7.05±0.89	2.55±0.66	0.42±0.06	0.43±0.06
Combination group (n=63)	6.84±0.88	2.03±0.47	0.40±0.06	0.53±0.09
t	1.286	4.975	1.806	6.993
P	0.201	<0.001	0.074	<0.001

and beta collagen degradation fragments (β-CTx), were measured in fasting venous blood collected at admission and three years post-operation. Serum BALP, 25-(OH)D, and β-CTx were detected using radioimmunoassay with an automatic electrochemiluminescence immunoassay (brand: Roche; model: Elecsys 2010).

6. Neuropeptide Y (NPY) and prostaglandin E2 (PGE2) levels were assessed using enzyme-linked immunosorbent assay at both admission and three years post-operation.
7. Complications in both groups within three years post-operation were documented.

Statistical analysis

This study utilized the SPSS 20.0 software package for statistical analyses on the collected data. Count data (%) were analyzed using the chi-square test and presented as c2. Measurement data were expressed as mean ± standard deviation (SD). The independent-samples t-test was employed for between-group comparisons of the measurement data, while the paired t-test was used for within-group comparisons, and the results were reported as t-values. A p-value <0.05 was considered statistically significant.

Results

Comparison of baseline data

The two groups did not differ significantly in age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, number of vertebral fractures, course of osteoporosis, injection amount of bone cement and injection method of bone cement (P>0.05, Table 1).

Comparison of vertebral body height and vertebral function

Upon admission, no significant differences were observed in vertebral body height and ODI score between the two groups (P>0.05). However, three years after surgery, the combination group exhibited a significantly greater increase in vertebral body height compared to the control group and achieved a significantly lower ODI score (P < 0.05, Table 2).

Comparison of pain degree and BMD

Upon admission, there were no significant differences in VAS score and BMD between the two groups (P>0.05). However, three years after surgery, the combination group demonstrated significantly lower VAS scores than the control group (P<0.05) and showed significantly higher BMD than the control group (P<0.05, Table 3).

Comparison of bone metabolism

Upon admission, the two groups did not differ notably in BALP, 25-(OH)D, and β-CTx levels (P>0.05). Three years after surgery, the combination group exhibited significantly lower levels of BALP and β-CTx and a significantly higher (25-(OH)D) level than the control group (P<0.05, Figure 2).

Comparison of NPY and PGE2

Upon admission, no notable differences were found in the NPY and PGE2 levels between the two groups (P>0.05).

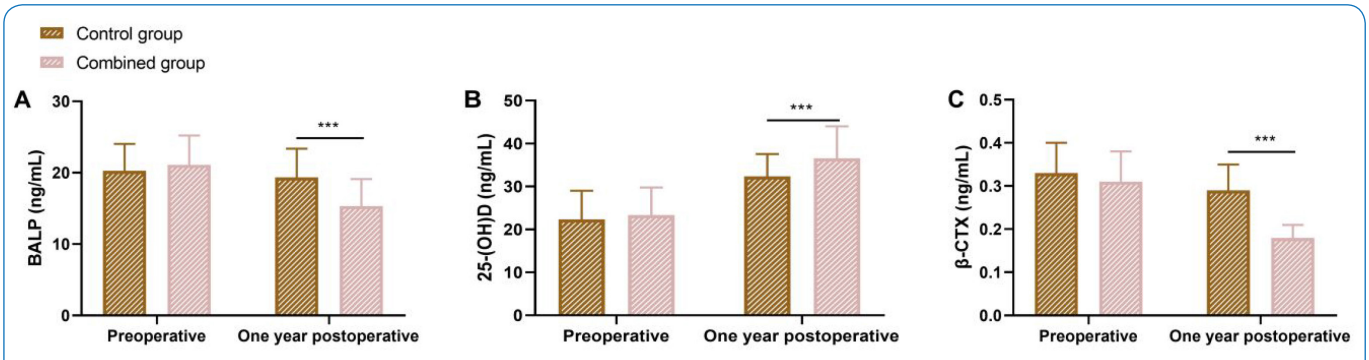

Figure 2. Comparison in the levels of bone metabolism indices between the two groups. A: Changes of BALP level between the two groups before and after operation. B: Changes of (25-OH)D level between the two groups before and after operation. C: Changes of β-CTx level between the two groups before and after operation.

Table 4. Overview of Complications.

	Bone cement extravasation	Re-occurrence of postoperative vertebral body fracture	Fever	Nausea	Total complication
Control group (n=55)	6 (10.91)	5 (9.09)	1 (1.82)	2 (3.64)	14 (25.45)
Combination group (n=63)	9 (14.29)	1 (1.59)	3 (4.76)	5 (7.94)	18 (28.57)
χ^2					0.144
P					0.704

However, three years after the operation, significantly lower levels of NPY and PGE2 were observed in the combination group compared to the control group (P<0.05, Figure 3).

Comparison of complications

The control group was not significantly different from the combination group in the total incidence of complications (25.45% vs. 28.57%, P>0.05, Table 4).

Discussion

The most distinguishing characteristic of osteoporosis is a decrease in bone density. This reduction in bone density leads to the deterioration of bone microstructure, resulting in increased bone fragility and susceptibility to fractures[13]. Nitrogen-containing bisphosphonates are considered first-line drugs for treating osteoporosis. They can form stable compounds by combining with calcium ions on the mineralized surface of bone, inhibiting the activity of bone resorption cells, and reducing the rate of bone resorption. By interfering with the survival and function of bone resorption cells and inhibiting bone resorption, these medications increase bone mineral density (BMD) and reduce the risk of osteoporotic fractures[14]. Zoledronic acid, a nitrogen-containing bisphosphonate, exerts a potent inhibitory effect on bone resorption, effectively enhancing the re-filling and re-mineralization of the reconstructed space. Consequently, it significantly reduces the occurrence of vertebral fractures[15]. Osteoporotic fractures are among the most serious complications of osteoporosis, particularly prevalent in elderly patients. Percutaneous vertebroplasty can increase the stability and strength of the vertebral body by injecting bone cement into the vertebral body. This process fixes and strengthens the fracture site, reduces pain, and restores the normal height of the vertebral body[16].

In this study, elderly patients with osteoporotic vertebral compression fractures (OVCF) received zoledronic acid infusion after undergoing percutaneous vertebroplasty. Consequently, their vertebral body height was significantly higher compared to patients who did not receive zoledronic acid, and their Oswestry Disability Index (ODI) score was significantly lower than that of the latter group. These results suggest that the combined application of percutaneous vertebroplasty and zoledronic acid is more effective in enhancing vertebral body height and improving spinal

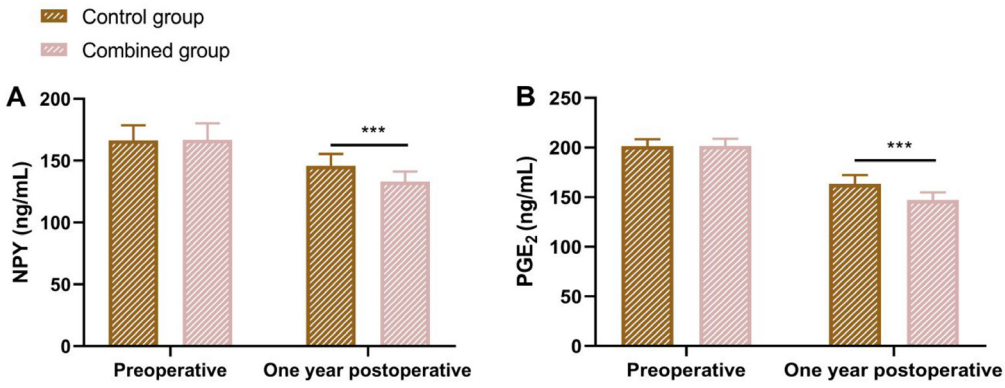

Figure 3. Comparison in the levels of NPY and PGE2 between the two groups. A: Changes of NPY level between the two groups before and after operation. B: Changes of PGE2 level between the two groups before and after operation.

function. Furthermore, concerning the pain degree and bone mineral density (BMD) of patients after treatment, our study found that the combined treatment significantly reduced the pain degree and increased the BMD of patients three years after the operation. This aligns with the findings of Tu et al.[17], who, in a retrospective study, demonstrated significant improvements in pain degree and ODI score in patients with osteoporosis treated with lumbar interbody fusion and zoledronic acid. The observed benefits can be primarily attributed to the interaction and synergistic effect of several key factors. Firstly, as a bisphosphonate, zoledronic acid effectively reduces bone resorption and increases BMD, thereby enhancing the stability of surgical outcomes and reducing the risk of future fractures. Secondly, procedures like vertebroplasty stabilize the damaged vertebral body by injecting bone cement. When combined with the ability of zoledronic acid to enhance the stability of the bone structure, it more effectively restores and maintains the structural integrity of the spine.

Furthermore, the combined treatment significantly alleviated pain associated with osteoporosis and facilitated the recovery of spinal function, as indicated by the patients' Oswestry Disability Index (ODI) scores. In comparison to zoledronic acid, teriparatide—acting as a recombinant human parathyroid hormone analog—directly enhances bone density by stimulating bone formation, presenting a distinct therapeutic mechanism. Teriparatide's advantage lies in its ability to promote new bone formation, particularly crucial in restoring bones that have been thinned or damaged by osteoporosis. While zoledronic acid offers long-term biological improvement by reducing bone resorption, teriparatide directly promotes bone formation, offering an alternative approach for enhancing bone after fracture treatment. This dual perspective highlights the complementary benefits of these two treatments in addressing osteoporosis-related complications.

BALP is a bone formation marker reflecting the activity of bone cells and the degree of bone formation[18]. β-CTx is a metabolite of bone resorption, and its level reflects the activity of bone resorption. A high level of β-CTx is associated with an increased risk of fracture[19]. 25-(OH)D is a key regulator of bone metabolism. Its deficiency reduces the absorption of calcium and phosphorus, subsequently lowering bone mineral density (BMD) and bone quality[20]. In this study, three years after the operation, the combination group exhibited notably lower levels of BALP and β-CTx and a significantly higher level of (25-OH)D than the group that underwent percutaneous vertebroplasty alone. These results indicate that the combination of zoledronic acid therapy can effectively reduce the destruction and bone loss of bone tissue, promoting its normal structure and function. The rationale may be attributed to percutaneous vertebroplasty stabilizing fractures and stimulating bone formation by injecting bone cement or grafting materials into the vertebral body, possibly triggering an active process of bone formation. The combined use with zoledronic acid inhibits bone resorption and promotes bone formation, achieving a more significant effect on bone metabolism. NPY and PGE2 are indices related to bone pain. Elevated NPY and PGE2 can promote the transmission and perception of pain in the spinal cord and surrounding tissues, causing persistent bone pain in fracture patients[21,22]. In this study, the inhibitory effect of combination therapy on NPY and PGE2 was more significant. This may be attributed to zoledronic acid reducing the process of bone resorption by inhibiting the activity of osteoclasts, potentially decreasing the release of inflammatory response and pain mediators caused by fractures and bone diseases, consequently reducing the production of NPY and PGE2[23,24]. Finally, a comparison of complications between the two groups revealed that zoledronic acid did not significantly increase the risk of complications after percutaneous vertebroplasty.

This study also has some limitations. Firstly, owing to the retrospective nature of the study, inherent biases may exist that cannot be entirely eliminated. Consequently, further prospective randomized controlled studies are essential to validate and confirm the conclusions drawn from this research. Secondly, the study lacks longer-term follow-up results, which poses a challenge in providing a comprehensive evaluation of the treatment effect. Therefore, conducting studies with extended follow-up periods would be valuable in assessing the long-term outcomes of the combined treatment approach.

In conclusion, the combined use of zoledronic acid and percutaneous vertebroplasty has proven effective in enhancing lumbar function, lumbar bone mineral density (BMD), and bone metabolism indices for elderly patients with osteoporotic vertebral compression fractures (OVCF). Furthermore, this combination treatment demonstrates a reduction in pain levels, as well as in the levels of neuropeptide Y (NPY) and prostaglandin E2 (PGE2).

Ethics approval

The study was approved by the Medical Ethics Committee of Chun'an County Hospital of Traditional Chinese Medicine (ID number: YLS2017055).

Authors' contributions

H.W. conceived and designed the study, and drafted the manuscript. J.Z. and G.Y. collected, analyzed, and interpreted the experimental data. L.Y. revised the manuscript for important intellectual content. All authors have read and approved the final manuscript.

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