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Original Research Article

Clinical efficacy of a combination of zoledronic acid and percutaneous vertebroplasty in spinal metastases and its influence on serum levels of bone loss markers

Shaokun Yang*, Bingguang Zuo, Guangning Ding
Cangzhou People's Hospital, Cangzhou, China

For correspondence:* ***Email:* *chongwcjaof46345@163.com*

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Abstract

Purpose: *To investigate the clinical efficacy of zoledronic acid plus percutaneous vertebroplasty in spinal metastasis, and its effect on serum levels of bone loss markers.*
Methods: *Sixty-two patients with spinal metastases were randomly divided into study group (n = 31) and control group (n = 31). The control group underwent percutaneous vertebroplasty, while study group received zoledronic acid plus. Analgesic effect, Japanese Orthopedic Association (JOA) score, improvement in movement ability, quality of life, carboxy-terminal cross-linked peptide of type I collagen (ICTP), procollagen type I N-terminal amino peptide (PINP), and bone-specific alkaline phosphatase (BALP) levels were compared between the two groups.*
Results: *The study group presented a higher degree of analgesic effectiveness and better performance than the control group ($p < 0.05$). After treatment, the Kamofsky function scores were increased in both groups, but it was higher in the study group ($p < 0.05$). After treatment, the JOA score of the study group was higher than the control group ($p < 0.05$). The post-treatment levels of ICTP, PINP and BALP decreased in both groups, but was markedly lower in the study group ($p < 0.05$).*
Conclusion: *A combination of percutaneous vertebroplasty and zoledronic acid is effective for the treatment of spinal metastasis. It enhances mobility, improves quality of life, reduces serum levels of bone loss markers, and produces good analgesic effect.*

Keywords: *Percutaneous vertebroplasty, Zoledronic acid, Spinal metastasis, Pain, Quality of life*

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INTRODUCTION

Spinal metastasis, one of the most common bone metastases in orthopedic clinics, affects the vertebral body, resulting in pathological fractures, bone pain, spinal cord compression and hypercalcemia. It affects not only the quality of life of patients, but also their survival, especially in severe cases [1]. Spinal metastasis is usually aggressive, a feature which makes it difficult to completely remove through surgical treatment. Therefore, primary cancer and metastasis are usually treated with chemotherapy, radiotherapy and drugs so as to preserve nerve function, relieve pain, and stabilize or correct the shape of the spine [2]. Vertebroplasty significantly reduces vertebral metastasis-induced pain, enhances the stability of the spine and strengthens the

vertebral body, and it is safe, simple and free from systemic adverse reactions [3]. Zoledronic significantly inhibits bone resorption caused by increased osteoclast activity acid by specifically acting on bone diphosphate compounds. Moreover, zoledronic acid selectively acts on bones and shows a high affinity for bone mineralization, making it the new standard treatment for cancer bone metastasis [4]. The aim of this study was to investigate the clinical efficacy of combination of zoledronic acid and percutaneous vertebroplasty in the treatment of spinal metastases, and its effect on serum levels of bone loss markers.

METHODS

Patients and procedures

This study enrolled 62 patients with spinal metastases in our hospital from January 2018 to January 2020 and randomly divided them into study group and control group, 31 cases in each group. This study was approved by Medical Science Research Ethics Committee of Cangzhou People's Hospital (approval no. 2017 (135)-152) and international guidelines for human studies were followed [5].

Inclusion criteria

The included patients were those who were diagnosed with bone metastasis through MRI or CT, X-ray and ECT, and patients who suffered from bone pain in line with the indications for vertebroplasty (in malignant spinal tumors, osteolytic bone metastases of spine and myeloma are usually painful, with multiple lesion foci, and it may be difficult for some patients in poor conditions to undergo surgery). One or two weeks of radiotherapy relieves pain in patients. Usually, if vertebroplasty is carried out, it immediately relieves the pain and increases the strength of the spine. Most spinal hemangiomas cause no symptoms at all. Thus, the occurrence of pain was an indication for the need for vertebroplasty. Patients signed a consent letter.

Exclusion criteria

Patients who had abnormal liver and kidney functions, patients who could not tolerate the treatments, and those whose previous endocrine therapy or chemotherapy was stopped for less than one month, were not enrolled in the study.

Surgical procedures

Patients in the control group underwent vertebroplasty. Before treatment, the patients were subjected to CT examination to measure the distance and angle between the skin and the lesion. Then, a surgery path was selected by avoiding important tissues and structures. All patients were in a lateral position under general anesthesia, and were operated on according to the surgical plan. After the patient was fixed with pedicle screws, the vertebral arch and small joints behind the diseased vertebrae were removed, and the visible tumor was scraped to a great extent, followed by insertion of the needle through the approach. When the needle point reached the target, a mixture of acrylic resin monomer and methacrylic resin polymer (in a ratio of 4:1) was injected into the diseased vertebral part. The study group was intravenously injected with zoledronic acid (Chia Tai Tianqing Pharmaceutical Group Co. Ltd., batch no. Zhunzi H20113138), 5 mg at a time, once every 28 days, and a total of 4 injections.

Clinical indices of treatment outcomes

The were 4 categories of analgesic effect viz: CR, PR, MR and NR [5]. Analgesic effect was classified as CR if patients had no pain at all, while PR was for significantly reduced pain, relative to pain before treatment, such that the patients lived normal lives, and their sleep was not generally affected by pain. Analgesic effect in MR grade was for patients whose pain was slightly relieved, relative to the situation before treatment, but their sleep was still disturbed. If there was no pain relief, the analgesic effect was classified as NR.

Improvement in movement was classified as *significantly effective* if movement ability was improved by ≥ two levels, compared to movement ability before treatment; *effective* if movement ability was improved by one level, relative to movement ability before treatment; or *ineffective* if there was no improvement or if there was a decrease in movement ability, when compared with movement ability before treatment [6]. The Kamofsky function scale was employed to assess the quality of life before and after treatment.

Lumbar vertebrae function was measured using the Japanese Orthopedic Association (JOA) scale [7]. In this scale, the full score for subjective symptoms was 9 points. These points covered low back pain, leg pain or numb pain, with scores ranging from 0 to 3 points. The full score for clinical signs was 6 points. These covered straight leg elevation test, sensory disorders and dyskinesia, and the scores ranged from 0 to 2 points, with muscle strength scoring from 0 to 3 points. The differences between the

two groups before and after treatment were compared.

The levels of ICTP, PINP, and BALP in the two groups were assayed with ELISA kits before and after treatment, and compared. These parameters were also determined one week after treatment.

Statistical analysis

Measurement data are expressed as mean ± standard error of the mean (S.E.M.), and were compared using independent paired *t*-test. Count data are expressed as numbers and percentages [n (%)], and were compared using χ2 test. All statistical analyses were done with SPSS23.0 statistical software. Values of $p < 0.05$ were taken as indicative of statistically significant differences.

RESULTS

Comparison of the general data

In the study group, there were 31 patients comprising 18 males and 13 females, and their ages ranged from 35 to 80 years (mean age = 50.03 ± 6.43 years). The 31 patients in the control group consisted of 17 males and 14 females, and their ages ranged from 34 to 81 years, with mean age of 49.58 ± 4.44 years. The baseline data of the two groups were comparable ($p > 0.05$). These baseline data are shown in Table 1.

Table 1: Comparative demographic profile (n = 31)

Group	Gender (Male/Female)	Age (years)
Study	18/13	50.03±6.43
Control	17/14	49.58±4.44
χ^2 /t	0.066	0.321
P-value	0.798	0.749

Effectiveness of pain relief

The effectiveness of pain relief in the study group (80.64%) was significantly higher than that in control group (41.94%; $p < 0.05$). As shown in Table 2.

Table 2: Comparison of the effective rate (n = 31)

Group	CR	PR	MR	NR	Total effective rate
Study	5	11	9	6	25 (80.64)
Control	2	6	5	18	13(41.94)
χ^2					9.789
P-value					0.002

Movement ability (mobility)

The movement improvement in the study group was 87.10 %, relative to 64.52 % in the control group ($p < 0.05$), as shown in Table 3.

Kamofsky function scores

After treatment, there were marked increases in the Kamofsky function scores of the two groups ($p < 0.05$). However, the study group had higher Kamofsky function score than the control group ($p < 0.05$). As shown in Figure 1.

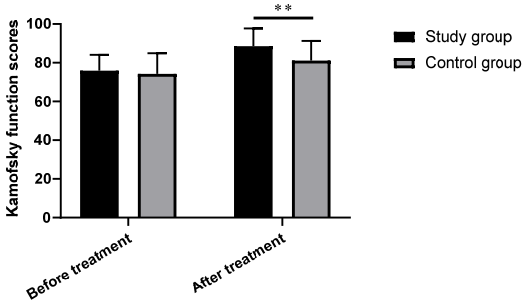

Figure 1: Comparison of Kamofsky function scores. $^{**}P < 0.01$

JOA scores

There were increases in the JOA scores of the two groups after treatment ($p < 0.05$). However, JOA score was higher in the study group than in the control group ($p < 0.05$). As shown in Figure 2.

Serum levels of bone loss markers

The serum levels of bone loss markers in the two groups were decreased after treatment ($p < 0.05$). However, there were higher decreases in bone loss markers in study group than in the control group ($p < 0.05$). As shown in Table 4.

Table 3: Comparison of movement improvement (n = 31)

Group	Significant Effective	Effective	Ineffective	Total effectiveness
Study	16	11	4	27(87.10)
Control	12	8	11	20(64.52)
χ^2				4.309
P-value				0.038

Table 4: Comparison of serum levels of bone loss markers (mean ± SD, n = 31)

Group	ICTP (μg/L)		PINP (ng/ml)		BALP(U/L)	
	Before treatment	***After treatment***	***Before treatment***	***After treatment***	***Before treatment***	***After treatment***
Study	8.70±0.27	5.35±0.14	132.55±15.98	83.86±14.89	653.58±27.94	493.45±27.60
Control	8.78±0.24	6.55±0.34	132.12±22.18	100.17±23.35	668.26±35.99	585.65±44.75
t	1.131	18.169	0.087	3.279	1.793	9.763
P-value	0.263	<0.001	0.931	0.002	0.078	<0.001

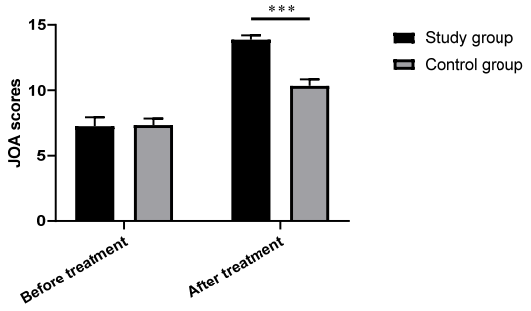

Figure 2: Comparison of JOS scores. ****P* < 0.001

DISCUSSION

Bone metastasis is a common complication in advanced cancers. Indeed, 30-85 % of cancer patients suffer from bone metastasis, mostly at the spine. A study has revealed that 5-10% of cancer patients have spinal metastasis which is seen in 90 % of patients who die of cancers [8]. Patients with spinal metastasis usually suffer from bone pain, pathological fractures, compressive myelopathy and paralysis which severely influence their quality of life [9]. It is generally known that tumors move to bone tissue, resulting in increased osteoclast activity and osteolysis. Thereafter, the tumor cells infiltrate into the periosteum and surrounding soft tissues, leading to pain. In addition, tumor cells or local inflammatory cells secrete inflammatory mediators such as PG, IL-1 and TNF which cause pain in patients through stimulation of nerve endings. Patients with spinal metastasis experience severe and long-lasting pain which cannot be relieved by analgesics, and some patients may undergo pathological fractures or compressive myelopathy, leading to paraplegia [10-12]. Therefore, there is need for these patients to receive effective treatment.

At present, it is difficult to radically remove spinal metastases. Consequently, treatment methods are focused on how to relieve the symptoms and improve the quality of life of the patients. These treatments involve radiotherapy, chemotherapy, surgery, radionuclide therapy and use of bisphosphonates. It has been reported that comprehensive treatment measures achieve the best efficacies [13]. Vertebroplasty enhances the physical stability of the infiltrated vertebra. The procedure is associated with decreased tissue damage and minimal invasiveness. It eliminates the stimulation of painful nerve endings due to friction and compression, thereby improving the quality of life of patients [14]. However, vertebroplasty is associated with complications like puncture injury, bone cement leakage and pulmonary embolism. Zoledronic acid, a new generation bisphosphonate drug with the strongest pharmacological activity so far, effectively inhibits the activity of osteoclasts. It directly blocks bone destruction by osteoclasts, inhibits the biosynthetic pathways of formaldehyde and valeric acid, and inhibits the activity of farnesyl pyrophosphate synthase, resulting in the inhibition of osteoclasts activity and induction of osteoclast apoptosis. Moreover, it inhibits the transformation of precursor cells into mature osteoclasts, and also blocks the synthesis of osteoclasts and the release of prostaglandins [15]. Zoledronic acid is used for relief of bone pain and pain from pathological fractures. It improves the quality of life of patients, and is beneficial for patients in whom other bisphosphonate drugs fail to achieve efficacy. Due to its high efficacy and short infusion time, zoledronic acid has become the new treatment option for bone metastases [16].

The results of this study showed that the combination of vertebroplasty with zoledronic acid relieved pain in patients with spinal metastases and enhanced movement ability. Thus, the combination treatment produced a great analgesic effect in patients with spinal metastases, consistent with the results of similar studies [17]. When bone cement is injected into vertebra, it mitigates compression fracture in patients with spinal metastases, enhances support of the bone trabecula, and stabilizes the vertebra. In patients with vertebral fracture, it rebuilds the stability of the spine, markedly improves its kyphosis and restores the height of the affected vertebra. In addition, the heat and cytotoxicity generated during bone cement polymerization not only promote necrosis of surrounding tumor cells, but also destroys nearby nerve endings, thereby effectively reducing pain. Zoledronic acid effectively inhibits osteoclast

activity and promotes apoptosis of osteoclasts, inhibits osteoclast synthesis and suppresses the release of interleukins and prostaglandins. It also binds to bone and prevents osteoclasts from dissolving cartilage and mineralized bone, and blocks the release of bone calcium due to a variety of stimulating factors from tumors [18,19]. This study has revealed that zoledronic acid reduced complications of cancer bone metastasis. Patients with spinal metastasis were treated with zoledronic acid, and the serum levels of new bone loss markers (ICTP, PINP and BALP) were determined. It was found that the serum levels of bone loss markers in the two groups were decreased after treatment, but more marked decrease was seen in the study group. The decreases in serum levels of bone loss markers may be due to the fact that zoledronic acid up-regulated osteoprotegerin (OPG) and down-regulated RANKL. In addition, the cannabinoid receptor type2 (CB2) and inverse agonist AM630 mitigated the pain caused by zoledronic acid in patients with spinal metastases, indicating that zoledronic acid reduced the pain and bone destruction through CB2 mediation [20].

Limitations of the study

First of all, the statistic results might be biased due to the small sample size plus the non-uniform baseline standards when selecting the samples. Second, the biological and histological characteristics of various primary malignant tumors and the degree of spinal disease at the time of treatment is inconsistent, which can cause statistical errors. The conclusions drawn in this study are only preliminary, and no further stratification and multivariate analysis of the cases was conducted. Further studies with a larger sample size, longer follow-up and more rigorous experimental design are needed to clarify the research conclusions.

CONCLUSION

The combination of zoledronic acid and percutaneous vertebroplasty is an effective treatment for spinal metastasis. It produces good analgesic effect, improves movement ability and quality of life of patients, and reduces serum levels of bone loss markers.

DECLARATIONS

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We 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 the authors.

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