

Percutaneous vertebroplasty combined with chemotherapy in the treatment of multiple myeloma patients with vertebral compression fractures

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Multiple myeloma (MM) is a hematologic malignancy in which plasma cells proliferate in the bone marrow, leading to osteolytic bone destruction. Bone involvement is present in up to 90% of patients with MM and is associated with pain and skeletal-related complications, such as pathologic vertebral compression fractures (VCFs).^[1] MM-associated VCFs cause spinal instability, back pain, spinal kyphosis, neurologic dysfunction, and subsequent respiratory complications, which markedly decrease the quality of life of affected patients.

Patients with MM-associated VCFs without neurological involvement can undergo vertebral augmentation, including percutaneous kyphoplasty (PKP) and percutaneous vertebroplasty (PVP).^[2] In recent years, preliminary studies have demonstrated the effectiveness of PVP or PKP in controlling the pain and improving the quality of life of patients with MM-associated VCFs.^[2] However, these studies have shortcomings of small sample sizes (24–108 patients) and short follow-up time (3–36 months). Most of these studies focused on clinical function, but few studies focused on complications and the incidence of long-term subsequent fractures after vertebral augmentation. This retrospective study aimed to evaluate the long-term clinical outcomes and complications of PVP combined with chemotherapy for MM-associated VCFs without neurological involvement.

This retrospective study cohort comprised 109 patients treated for MM-associated VCFs without neurological involvement between January 2010 and December 2017. Sixty-four patients underwent PVP and chemotherapy (combined therapy group), while 45 patients received chemotherapy alone (chemotherapy group). All patients

presented with severe back pain and were diagnosed with pathological VCFs based on radiography, computed tomography, and magnetic resonance imaging. All patients had acute pain that was not responsive to various analgesics. The diagnosis of MM was based on bone marrow aspiration or biopsy. Vertebral biopsy during vertebroplasty also confirmed myeloma infiltration in the fractured vertebrae. All patients had no neurological deficits, and magnetic resonance imaging showed no evidence of bone destruction in the posterior wall of the vertebral body or compression of the spinal cord or nerve roots in all patients. The bone mineral density of 2 body sites, lumbar spine (L1–L4, excluding pathological vertebrae), and the right femur, was measured by dual-energy X-ray absorptiometry (Hologic Discovery, Bedford, MA, USA). The corresponding lower T-score of the 2 body sites was calculated. The diagnostic criteria for osteoporosis were T-score ≤ -2.5 .

All 64 patients in the combined therapy group underwent PVP with a bone cement vertebroplasty system (Stryker, Kalamazoo, MI, USA). C-arm fluoroscopy was used for real-time needle positioning and adjustment, and for continuous monitoring during cement injection. PVP was performed by the unilateral transpedicular approach under local anesthesia (1% lidocaine) with the patient in the prone position, as previously described. A biopsy needle was used to obtain the biopsy material under fluoroscopic control to confirm the diagnosis of MM. A mixture of polymethylmethacrylate (Stryker, Kalamazoo, MI, USA) and barium was then injected into the vertebral body through the cannula under fluoroscopic control. Extreme care was taken to prevent bone cement leakage during the injection. An

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average of 3.5 mL (range, 2.0–5.5 mL) of bone cement was injected into each of the compressed vertebrae. All patients were treated with chemotherapy (mainly based on bortezomib or lenalidomide), bisphosphonates (zoledronic acid administered intravenously once a month for 1 year), and general supportive therapy in accordance with the guidelines for the diagnosis and management of MM.^[3] Both groups were instructed to wear a brace for 3 months after treatment.

Demographic data, fracture locations, and injected levels were recorded. The International Staging System stage, which is used to predict the outcome and overall survival of patients with MM, was also recorded.^[3] Pain was evaluated using a ten-point visual analogue scale (VAS) where 0 represented no pain and 10 represented the worst possible pain. Quality of life was measured by the Oswestry Disability Index (ODI), which represents the level of disability on a scale ranging from 0% (no disability) to 100% (bed-bound). Each clinical variable was recorded before treatment, at 1 day, 1 month, 6 months, and 12 months after treatment, and at final follow-up. The radiographs of all patients in the combined therapy group were reviewed at 1 day after PVP for evidence of cement leakage and pulmonary complications. Follow-up was completed by clinical interview (1 month after PVP or chemotherapy) and phone interview (at 6 months, 12 months, and every 12 months thereafter). A clinical interview with radiological imaging was performed if a patient reported new-onset back pain. Subsequent vertebral fractures that occurred after treatment were recorded. Continuous variables (including the VAS and ODI) were presented as the mean ± standard deviation. The clinical data were compared between the 2 groups using the chi-squared test and independent-sample *t* test. The VAS and ODI at different follow-up timepoints were compared with baseline (pre-operatively) using the paired *t* test. All data were analyzed using SPSS 22.0 statistical software (IBM, Chicago, IL, USA). A value of *P* < 0.05 was considered statistically significant.

A total of 109 patients (mean age, 72.6 ± 7.3 years; range, 50–85 years) were available for evaluation after a mean follow-up time of 4.5 years (range, 36–67 months). There

were no significant differences between the 2 groups in sex, age, number of fractured vertebrae, International Staging System stage, VAS, and ODI (all *P* > 0.05). Out of 109 patients, 76 (69.7%) suffered from osteoporosis. The differences of bone mineral density T-scores and proportion of osteoporosis were not significant between the 2 groups (both *P* > 0.05). There were 59 patients with single-level vertebral fractures, 39 with two-level vertebral fractures, and 11 with three-level vertebral fractures; the proportion of each type of vertebral fracture did not significantly differ between the 2 groups. The combined therapy group had a total of 100 affected vertebrae, of which 53 were thoracic vertebrae and 47 were lumbar vertebrae. The chemotherapy group had a total of 69 affected vertebrae, of which 38 were thoracic vertebrae and 31 were lumbar vertebrae; the distribution of vertebral fractures did not significantly differ between the 2 groups.

The VAS of the combined treatment group decreased significantly from 7.7 ± 1.3 pre-operatively to 2.2 ± 0.9 on post-operative day 1 and became lower at each follow-up timepoint, with each subsequent VAS significantly lower than the baseline value. In the chemotherapy group, the VAS was not significantly decreased at 1 day after treatment compared with baseline, but decreased significantly from 7.6 ± 1.0 before treatment to 5.2 ± 0.8 at 1 month after treatment, and then continued to decline at each follow-up timepoint. The VAS significantly differed between the combined treatment group and the chemotherapy group at 1 day, 1 month, and 6 months after treatment, but not at 12 months (2.7 ± 0.7 vs. 2.9 ± 0.6, *P* > 0.05) and final follow-up (2.9 ± 0.7 vs. 3.1 ± 0.7, *P* > 0.05) [Figure 1A]. The ODI showed a similar decrease after treatment to that of the VAS in both groups. The ODI was significantly lower in the combined treatment group than the chemotherapy group at 1 day (57.3 ± 11.4% vs. 76.3 ± 17.3%), 1 month (29.5 ± 8.9% vs. 57.1 ± 12.5%), and 6 months after treatment (33.2 ± 8.7% vs. 36.9 ± 8.4%) (all *P* < 0.05). However, the ODI did not significantly differ between the combined treatment group and the chemotherapy group at 12 months (27.4 ± 7.4% vs. 30.3 ± 7.6%, *P* > 0.05) and final follow-up (30.5 ± 6.7% vs. 32.6 ± 7.6%, *P* > 0.05) [Figure 1B].

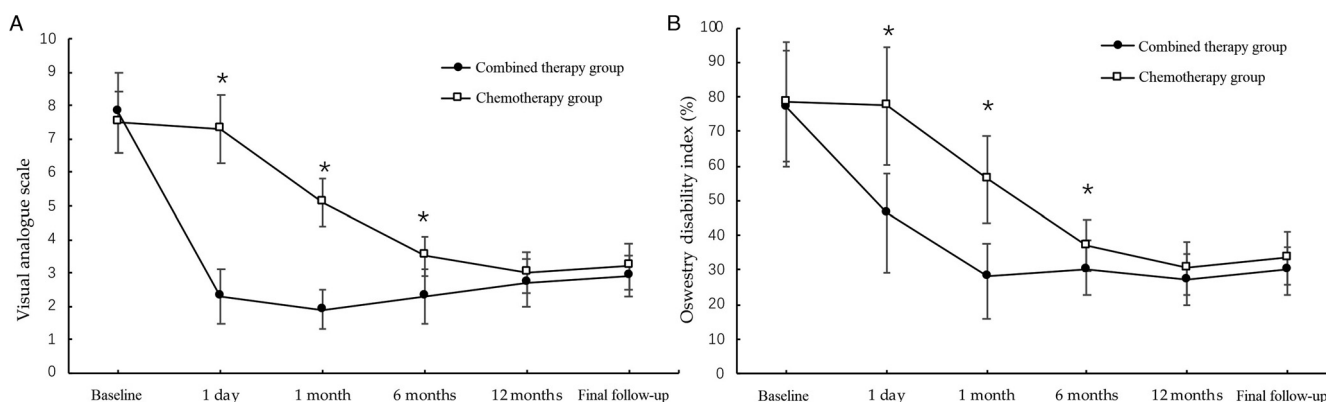


Figure 1: Mean VAS and ODI in the 2 groups over time. (A) The mean VAS significantly differed between the 2 groups at 1 day, 1 month, and 6 months after treatment, but not at 12 months and final follow-up. (B) The mean ODI was significantly lower in the combined treatment group than the chemotherapy group at 1 day, 1 month, and 6 months after treatment, but there were no significant intergroup differences at 12 months and final follow-up. Statistically significant difference. ODI: Oswestry Disability Index; VAS: Visual analogue scale.

In terms of clinical outcomes, the combined therapy achieved immediate pain relief and improved activity that was superior to that of chemotherapy alone. This suggests that PVP improved quality of life by providing optimal and rapid pain relief. In contrast, the pain relief in the chemotherapy group was slow and indistinct, which might affect the daily activities of patients and increase the risk of complications such as pneumonia, deep vein thrombosis, and bedsores, leading to the interruption of chemotherapy. However, these clinical outcomes did not significantly differ between the 2 treatment groups at 12 months and final follow-up. These results were similar to other studies.^[2] The mechanism of pain relief after vertebroplasty is still unclear, and may involve several factors. First, bone cement stabilizes the microfracture and increases the strength of the vertebrae; second, the heat effect of bone cement destroys the pain receptors and nerve endings in the vertebrae; third, the cytotoxic effect of bone cement directly causes tumor cell necrosis; and finally, the injection of bone cement into tumor tissue cuts off the blood supply to induce tumor necrosis.

The major complication of PVP is bone cement leakage, with an incidence as high as 37.9% in patients with cancer-related VCFs; however, cement leakage is asymptomatic in most cases.^[2] In the present study, bone cement leakage occurred in 10 patients (15.6%), the cement leaked through the vertebral inferior endplate into the disc in 5 patients, leaked into the paravertebral vessels in 3 patients, and leaked to the lateral side of the vertebral body in 2 patients. However, none of these leakages led to clinical neurological symptoms or revision surgery. Furthermore, there were no other complications related to PVP, indicating that PVP was a relatively safe minimally invasive operation for MM-associated VCFs. The extravasated bone cement was mainly located in the intervertebral disc and paravertebral tissue, and there was no leakage into the spinal canal. We reduced the occurrence of bone cement leakage by accurately positioning the puncture needle and injecting the bone cement slowly and gently rather than forcefully. During the procedure, the whole injection process was carefully monitored to prevent the occurrence of cement leakage as much as possible. An average of 3.5 mL of bone cement was used for each injected vertebra in our study, as a cement volume of >4 mL reportedly results in an increased number of complications.

The incidence of subsequent VCFs after PVP in osteoporotic patients is 16.0%, the adjacent segment VCFs accounted for 51.6%,^[4] and up to 48.8% of the subsequent VCFs occurred within 3 months after PVP.^[5] However, the incidence of subsequent VCFs in patients with MM might differ from that in osteoporotic patients because of the different pathological type of fracture in these patient populations. In the present study, only 69.7% (76/109) patients suffered from osteoporosis, and the incidence of subsequent VCFs was 13.8% (15/109) during 4.5 years follow-up. Unlike osteoporotic subsequent VCFs, only 6 patients (40.0%) in the present study had adjacent subsequent VCFs, and 2 patients (22.2%) developed subsequent VCFs within 3 months after PVP. These results suggest that the new fractures

might be the result of the progression of MM rather than the PVP procedure itself. There was no recurrence of vertebral fracture in the combined therapy group, suggesting that bone cement adequately replaced the tumor tissue to fill the vertebral defect, stabilize the vertebral body, and avoid further destruction and collapse. During a mean follow-up of 4.5 years (range, 36–67 months), 23 (21.1%) patients died from MM-related organ failure (mainly from pneumonia, sepsis, and cardiovascular accidents), including 13 (20.3%) in the combined therapy group and 10 (22.2%) in the chemotherapy group ($P = 0.81$). The main causes of death were organ failure and severe infection due to the progression of MM. These results also indicate that PVP did not reduce the mortality rate.

In conclusion, the present study confirmed that PVP was a safe and effective minimally invasive treatment for painful MM-associated VCFs. Compared with chemotherapy alone, PVP combined with chemotherapy can improve quality of life by providing optimal and rapid pain relief, and this advantage can last for at least 6 months.

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Conflicts of interest

None.

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