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# Analysis of radiologic and clinical outcome in acute osteoporotic vertebral compression fracture: Single-agent teriparatide vs. teriparatide with subsequent vertebroplasty☆

Yongjun Jin *

*Department of Neurosurgery, Inje University College of Medicine, Seoul Paik Hospital, Seoul, South Korea*

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ABSTRACT

*Objectives:* To analyze the difference in union and clinical outcomes between teriparatide (T) and teriparatide with vertebroplasty (V) treatment modalities in osteoporotic vertebral compression fractures (OVCFs).
*Methods:* Patients were divided into two groups (T and V: 87 and 92 patients with 105 fractures each). Radiological features (fracture type/grade, presence of fracture gap/intravertebral vacuum cleft (IVVC)/posterior vertebral wall fracture, change in compression rate (CR)/kyphotic angle (CA), and fusion status) were assessed with 3D-CT at 3 and 6 months. The outcome was divided into success or failure based on visual analog scale (<3), absence of percussion tenderness on the spinous process, and pain during motion. Univariate and multivariate analyses were performed to identify risk factors for nonunion and failed outcomes in each group.
*Results:* The V group showed more favorable results than the T group at 3 months (CR>10%, 58% vs. 17%; CA>5°, 36% vs. 16%; union, 66% vs. 91%; successful outcome, 77% vs. 94%). At 6 months, no significant change was detected in CR and CA. A significant difference remained in union (89% vs. 100%) and successful outcomes (79% vs. 100%). The V group with age (>75 years) and initial CR (>40%) had more benefits than the T group in the subgroup analysis. In multivariate analysis for the T group, nonunion risk factors were hypertension (P = .0054) and fracture gap (P = .0075). IVVC (P = .047) was the sole risk factor for failure.
*Conclusions:* Teriparatide with subsequent vertebroplasty can be selected as the first-line treatment with better sequelae and outcomes in acute osteoporotic compression fractures.

## 1. Introduction

As human life expectancy increases, geriatric quality of life has become even more critical. The prevalence of osteoporotic compression fractures is increasing. These fractures are highly associated with poor outcomes (nonunion, malunion, vertebral collapse with a subsequent kyphotic deformity, need for revision surgery, acute and chronic pain, and disability in daily activities). The goals of treatment include reduction of pain and enhancement of union rate. However, painful spinal deformities and global sagittal imbalances have also been ignored as serious sequelae. Therefore, overcorrecting or maintaining the sagittal segmental angle in the early period should be considered more critically.

Anabolic agents such as teriparatide (TPTD) are preferred over pain medications. However, it does not assure immediate spinal stability. TPTD with subsequent vertebroplasty (VP) compensates for this problem and provides some degree of immediate pain relief. Therefore, knowing which combination of treatments results in lesser pain, higher fusion rate, lower compression rate, and lower kyphotic change is essential. Three-dimensional CT (3D-CT) scans were primarily used every three months to measure precise changes in the compression rate, kyphotic degree, and trabecular and cortical bone union. The objective of this study was to compare the radiological features and clinical outcomes between the T group treated with TPTD only and the V group treated with TPTD with subsequent VP in osteoporotic vertebral compression fracture patients.

## 2. Materials and methods

Consecutive patients with osteoporotic compression fractures were enrolled between 2014 and 2021. The Institutional Review Board of Seoul Paik Hospital, Inje University approved the study (No. 2021-09-002) and waived the requirement for individual consent since the

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* Department of Neurosurgery, Seoul Paik Hospital, Inje University College of Medicine 04551, Mareunnae-ro 9, Jung-gu, Seoul, South Korea.
*E-mail addresses:* jyj0819@gmail.com, jyj0819@hanmail.net.

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**Abbreviation lists**

| | |
|---|---|
| T | teriparatide |
| V | teriparatide with vertebroplasty |
| OVCFs | osteoporotic vertebral compression fractures |
| IVVC | intravertebral vacuum cleft |
| CR | compression rate |
| CA | kyphotic angle |
| 3D-CT | three-dimensional computed tomography |
| TPTD | teriparatide |
| VP | vertebroplasty |
| BMI | body mass index |
| T/TL/L | thoracic/thoracolumbar/lumbar |
| PVWF | posterior vertebral wall fracture |
| T1BM | degree of bone marrow signal change on T1-weighted mid-sagittal image |
| VHt | fractured vertebral height |
| DEXA | Dual-energy X-ray absorptiometry |
| MR | Magnetic Resonance |
| POB | the formation of a paravertebral osseous bridge |
| ΔCR | The differences in compression rate |
| ΔCA | The differences in Cobb's angle |
| VAS | visual analog scale |
| NEJM | New England Journal of Medicine |
| SMD | a standardized mean difference |

study is a retrospective analysis. Under the guidance of the National Health Insurance Service, conservative management for two weeks precedes other invasive treatments in patients under the age of 80. VP can be permitted when the progression of collapse and kyphotic angulation is confirmed using follow-up imaging. Elderly patients aged ≥80 years or patients with underlying diseases such as congestive heart failure, pneumonia, thrombotic phlebitis, uncontrolled diabetes mellitus, and chronic kidney disease requiring dialysis are exempt from this regulation. VP can be performed earlier. The decision of the VP was made based on the willingness of patients after informing them of the two treatment options.

### 2.1. Enrollment of patients

A total of 245 patients with osteoporotic compression fractures were recruited for this study. Among them, 66 patients were excluded because of surgical treatment, no history of TPTD treatment, absence of a 3D-CT scan, loss of follow-up, spondylitis conversion, and death. The enrolled subjects were divided into two groups (T group: 87 patients with 105 fractures; V group: 92 patients with 105 fractures). All patients were given the same prescriptions of teriparatide (TPTD, Forsteo, Eli Lilly and Company, USA), intramuscular injection of vitamin D (cholecalciferol 5 mg/ml, 200,000 IU, Vitamin D3 BON Injection, Kwang Dong Pharmaceutical Co., South Korea), and oral supplement of vitamin D plus calcium (cholecalciferol concentrated powder 4 mg + calcium carbonate 1250 mg as 500 mg calcium, twice a day, Bonky Cal-D chewable, Yuyu Pharmaceutical Co., South Korea) on admission.

### 2.2. Principle of vertebroplasty technique

In the V group, one spine surgeon performed the bilateral transpedicular approach in all cases. The Jamshidi needle tip should be placed around the fractured trabecular bone to fill the bone cement into the fracture site or fracture gap and prevent a lump-like filling pattern. In addition, the tip should also be located at the anterior one-third of the body in the sagittal plane to avoid ventral epidural leakage and obtain sufficient anterior column support. A small degree of intradiscal and paravertebral leakage was intended to achieve complete filling of the trabecular bone around the fracture site. Attempts were made to inject the same amount of cement via each transpedicular route. Finally, a small amount of cement was inserted into the middle column while the needle was withdrawn. The same technique was applied to all patients to reduce the confounding effects of cement's spatial distribution and interdigitation.

### 2.3. Demographic data on admission

The variables evaluated were sex, age, body weight, height, body mass index (BMI), comorbidities, T-score, 25-OH vitamin D level, fracture onset, location (T/TL/L), fracture type, fracture grade (0/0.5/1/2/3), fracture gap (none/small/large), intravertebral vacuum cleft (IVVC), posterior vertebral wall fracture (PVWF), degree of bone marrow signal change on T1-weighted mid-sagittal image (T1BM), fractured vertebral height (vHt), compression rate(CR), and Cobb's angle (CA) (Figs. 1 and 2).

Cellular processes in fracture healing are expected to develop in the early inflammatory stage (the first 2 weeks post-injury).[1] Without proper healing in that period due to steroid use or chronic preexisting illness, an unfavorable outcome would be anticipated. Past medical history, including diabetes mellitus, hypertension, hyperlipidemia, chronic kidney disease, and present history of steroid use, were searched. Dual-energy X-ray absorptiometry (DEXA) and vitamin D were used to evaluate osteoporosis.

Fracture onset was classified as acute (less than 2 weeks), subacute (2–4 weeks), and chronic (over 4 weeks). The location of the fracture was classified as thoracic, thoracolumbar (T11-L2), and lumbar. This geographic position was related to the innate segmental angle of the vertebral body and regional sagittal alignment; therefore, the anticipation of an unsatisfactory result is associated with a higher fracture location. The fracture types were classified as wedge deformity, biconcave deformity, and crush deformity based on Genant et al's study.[2] In case of bone marrow signal change on Magnetic Resonance (MR) imaging without definite vertebral collapse, insufficiency fracture type was added to this classification. Fracture grades were determined according to the study by Genant et al (CR<20%, grade 0.5; 20–25%, grade 1; 26–40%, grade 2; and >40%, grade 3). The classifications mentioned above represent the degree of spinal instability in load transmission; instability during motion may prevent fractured trabecular bone from achieving proper bony union.

The fracture gap, defined as the three-dimensional discontinuity of trabecular bone without gas attenuation on 3D-CT, was divided more specifically into none, small, and large, based on volume (Fig. 1A). This lesion may be filled with a cartilaginous callus, the development of which depends on the amount of motion at the fracture site, which ossifies into bone once the fracture has been sufficiently stabilized.[3] The larger the fracture gap, the more cartilage and lesser bone develop in the immature calluses. IVVC was defined as the presence of gas (principally nitrogen) attenuation along the fracture line of the vertebral body (Fig. 1B).[4] This sign is mostly suggestive of ischemic necrosis or osteonecrosis. The presence of IVVC is expected to influence unfavorable outcomes following delayed healing or nonunion. PVWF, defined as the protrusion of the posterior vertebral margin into the ventral epidural space, represents a failure of the middle column, which is thought to maintain spinal stability and sustain ongoing fracture healing (Fig. 1D).

MR imaging was conducted to discriminate between acute and chronic fractures and to assess T1BM, representing the possibility of trabecular absorption or further collapse in the fractured vertebral body

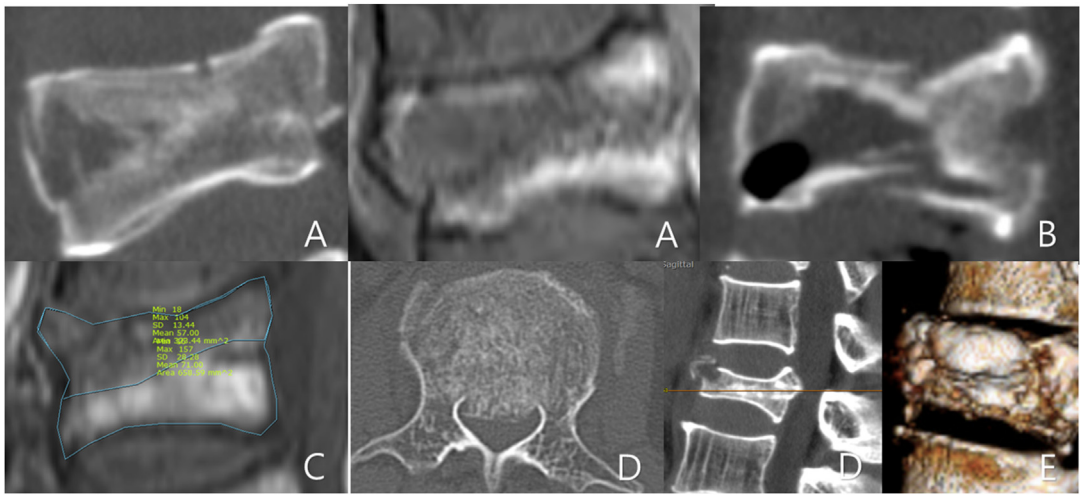
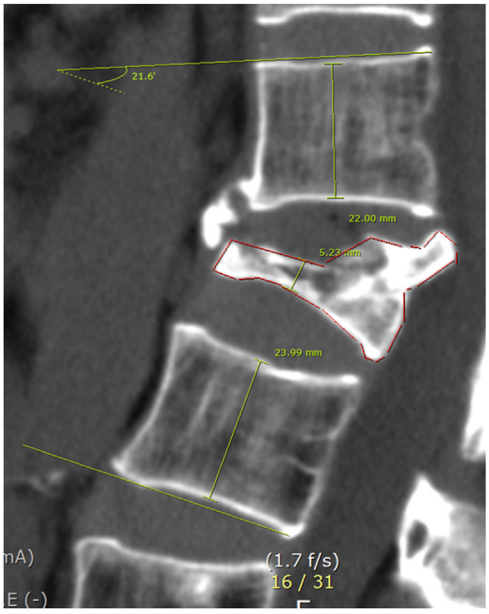



**Fig. 1.** A. Fracture gap on the sagittal plane of CT scan and MR T1WI revealed hematoma or soft callus in the acute phase. B. Intravertebral vacuum cleft (IVVC) on CT scan showed gas formation, which mean osteonecrosis in the chronic phase. C. Bone marrow edema can be seen around the fracture line on MR T1WI. D. Posterior vertebral wall fracture (PVWF) was demonstrated on the axial and sagittal plane of CT scan. E. Paravertebral osseous bridge (POB), which developed in the periosteum of residual anterolateral body, was identified on 3D-reconstructed CT scan.




**Imaginary vertebral height**

**=(upper + lower mid-body Ht)/2**

**CR (compression rate, %) at 0M =**

$$\left(1 - \frac{\text{Lowest body height of fractured body}}{\text{imaginary vertebral Ht (vHt)}}\right)$$

**CA (Cobb's angle, ° ) at 0M =**

**The angle between**
**the upper endplate of the upper body**
**and**
**the lower endplate of the lower body**

**Fig. 2.** Measurement of compression rate (CR) and Cobb's angle (CA).

(Fig. 1C). It was measured as follows: T1BM = (area with low signal intensity in contrast to fatty marrow with high signal/whole area in the fractured body) × 100(%). T2-weighted sagittal images with fat suppression were excluded due to concerns of overestimation.

### 2.4. Assessment of radiological parameters during follow-ups

Plain radiographs were obtained in the supine position on admission due to fracture-related pain. Follow-up X-rays were obtained in a standing position at 2 weeks, 1, 3, and 6 months. In addition, 3D-CT scans were taken on admission, 3 and 6 months for the evaluation of fracture type/grade, fracture gap, IVVC, PVWF, vHt, CR, and CA; the formation of a paravertebral osseous bridge (POB); and the status of the union on radiography.

The pre-fracture imaginary vHt was calculated as the mean value between the adjacent intact vertebrae above and below the fractured vertebra (Fig. 2). In the case of a previous adjacent vertebral fracture, only intact vertebral bodies were used. Fractured vHt was defined as the lowest height on the midsagittal plane despite minor asymmetry of vertebral collapse in the coronal image. To standardize and compare changes at different fracture levels, CR on admission was calculated as the percentage difference between imaginary vHt and fractured vHt (Fig. 2). CA was measured using the same endplate corners of the fractured body as reference points on the same midsagittal images acquired during admission and other follow-up periods (Fig. 2). The differences in the measurements (ΔCR and ΔCA) between admission and other follow-up periods were assessed. The ΔCR was classified as >10%, >15%, and >20%. ΔCA was divided into >5°, >10°, and >15°.

Paravertebral osseous bridge (POB) formation was defined as new bone formation initiated from the paravertebral cortical wall, particularly in the vicinity of the anterior longitudinal ligament (Fig. 1E). In cases of fracture, new bone formation seems to occur in the periosteal callus,[5] which may be related to a compensatory response to segmental instability. The incidence was evaluated to analyze its pathogenesis.

Strict binary analysis for union status was required to compare the two groups and search for risk factors. Radiologic union on the 3D-CT scan was evaluated in many aspects, including the complete absence of cortical discontinuity after bone remodeling in the anterior and posterior vertebral margin, osteosclerosis around the fracture line or bone cement in the trabecular bone without gas attenuation, or the gap between cement and osteosclerosis, and a substantial reduction (nearly over 90%) of the previous fracture gap. If radiologic findings fulfilled all conditions, the union was determined. In the case of residual endplate cortical disruption accompanying the formation of an incomplete POB between the fractured body and other intact bodies, this situation was defined as nonunion.

### 2.5. Assessment of clinical outcome

Binary clinical outcomes were divided into success and failure groups. A successful outcome was defined as a visual analog scale (VAS) score of less than 3 at 3 and 6 months, the absence of percussion tenderness on the spinous process of the fractured vertebra, and the absence of the provocative back pain at the level of fracture during flexion-extension/standing from sitting. These strict criteria were designed to distinguish fracture-related pain from confounding factors, such as preexisting paraspinal muscular pain, facetogenic back pain, and discogenic back pain. Percussion tenderness is an intuitive measure. Pain during motion changes may originate from micromotion owing to an incomplete union. One spinal surgeon assessed all three aspects in the same manner.

### 2.6. Complications after vertebroplasty

The incidence of cement leakage, refracture (>15% decrease in body height and 8° decrease in kyphotic angle as suggested by Yang et al6), and subsequent fracture (adjacent and non-adjacent) were assessed. These were based on the radiologic findings of X-rays, CT scans, and MR at the follow-up periods.

### 2.7. Statistical analysis

A single rater (YJJ) with more than 15 years of expertise in spinal surgery assessed all the images twice. An interval of 3 months was used between repeated measurements owing to corresponding follow-up visits to the outpatient clinic. IBM SPSS Statistics (version 28.0.0.0 (190), IBM Corp, Armonk, NY, USA) was used for all the statistical analyses. The average pairwise Cohen's kappa test was used to determine intraobserver reliability. The Landis and Koch guidelines were used to categorize the kappa value and define the strength of agreement, with values of 0.81–1.00, 0.61–0.80, 0.41–0.60, 0.21–0.40, and 0–0.20, indicating excellent, substantial, moderate, fair, and slight agreement, respectively.[7]

Student's t-test to compare differences between groups and paired t-test to confirm the measurement change in the same subject were used in univariate analysis of continuous variables. Bivariate correlation analysis was used to evaluate the interdependency among pretreatment continuous variables and the progression of CR and CA in the T group. Pearson's chi-square test was used to examine the differences between the groups in the univariate analysis of pre-treatment and post-treatment categorical variables. In particular, linear-by-linear association was executed to evaluate the dose–response relationship of outcome or union according to the stratified categories. Multiple linear regression and binary logistic regression analyses were used to identify the risk factors influencing failed union and unfavorable outcomes.

## 3. Results

### 3.1. Reliabilities of continuous variables

The intraobserver reliabilities of T1BM, pre-fracture imaginary vHt, fractured vHt, CR, and CA, ranged between 0.85 and 0.92 kappas. Thus, an intraobserver agreement was excellent for all variables.

### 3.2. Demographic differences between both groups

The V group had higher age (76 years vs. 67years), lower T-score (−3.1 vs. −2.7), higher incidence of hyperlipidemia (23% vs. 6%), later onset (10 days vs. 6 days), higher fracture grade (1.71 vs. 1.37), lower vHt (14.7 mm vs. 15.9 mm), more severe CA (2.5° vs. −2.0°), larger T1BM (65% vs. 54%), and more fracture gap (57% vs. 34%) between the two groups (Table 1). However, no statistically significant difference was found in the pre-treatment CR.

### 3.3. Interval changes of CR and CV during the follow-up period

Each group showed significant increases in ΔCR and ΔCA between 0 and 3 months (Table 2). After 3 months, the amount of change gradually decreased. This means that a follow-up period longer than 6 months is not necessary.

### 3.4. Intergroup comparison of radiologic and clinical results

The T group revealed higher ΔCR than the V group at the 3-month follow-up (Table 3). A more severe ΔCA was also observed in the T group; however, the intergroup change was not significant. This is because vertebroplasty may prevent the fractured body from collapsing, despite being more kyphotic in the V group on admission. After stratification, these findings of ΔCR>10% (58% vs. 17%) and ΔCA>5° (36% vs. 16%) supported this assumption. The incidence of POB was higher in the

**Table 1**
Baseline Characteristics of T and V group each.

| | T group | V group | p |
|---|---|---|---|
| No. of cases | 105 | 105 | |
| Sex (M:F) | 35:70 | 25:80 | 0.127 |
| Age (yr) | 66.70 ± 10.55 | 76.28 ± 10.20 | **0.000** |
| Bwt (kg) | 57.30 ± 8.31 | 57.19 ± 11.23 | 0.939 |
| Ht (cm) | 157.38 ± 8.29 | 155.73 ± 8.41 | 0.154 |
| BMI (kg/m$^2$) | 23.11 ± 2.71 | 23.55 ± 3.92 | 0.348 |
| T score | −2.73 ± 1.20 | −3.14 ± 1.19 | **0.012** |
| DM (%) | 16.2 | 21.9 | 0.292 |
| HTN (%) | 43.8 | 57.1 | 0.053 |
| hyperlipidemia (%) | 5.7 | 22.9 | **0.000** |
| CKD (%) | 1.0 | 2.9 | 0.313 |
| Steroid Mx (%) | 1.9 | 1.9 | 1.000 |
| 25-OH vit D (ng/ml) | 18.95 ± 11.79 | 18.46 ± 10.16 | 0.770 |
| onset (days) | 6.00 ± 10.46 | 10.33 ± 15.79 | **0.020** |
| onset (acute/subacute/chronic) | 89/10/6 | 75/17/13 | **0.021** |
| Location (T/TL/L) | 10/69/26 | 11/74/20 | 0.383 |
| Location (TL/others,%) | 66.7 | 70.5 | 0.552 |
| Type (insufficiency/wedge/biconcave/crush) | 4/68/4/29 | 3/60/8/34 | 0.277 |
| Fracture grade (0/0.5/1/2/3) | 2/38/20/30/15 | 0/31/12/34/28 | **0.011** |
| vHt 0M (mm) | 15.94 ± 3.60 | 14.70 ± 3.54 | **0.013** |
| CR 0M (%) | 25.51 ± 15.81 | 29.48 ± 15.63 | 0.069 |
| CA 0M (°) | −2.01 ± 15.62 | 2.45 ± 14.72 | **0.035** |
| T1 bone marrow signal change (T1BM,%) | 54.49 ± 21.71 | 64.62 ± 20.26 | **0.001** |
| Fracture gap (%) | 34.3 | 57.1 | **0.001** |
| Fracture gap (none/small/large) | 69/22/14 | 45/32/28 | **0.001** |
| IVVC (%) | 6.7 | 12.4 | 0.158 |
| posterior vertebral wall fracture (PVWF,%) | 27.6 | 32.4 | 0.451 |

The bold font indicates a statistical significance ($p < .05$). M denotes male, F female, Bwt body weight, Ht height, BMI body mass index, DM diabetes mellitus, HTN hypertension, CKD chronic kidney disease, Mx medication, T thoracic, TL thoracolumbar, L lumbar, vHt vertebral height, CR compression rate, CA Cobb's angle, and IVVC intravertebral vacuum cleft.

**Table 2**
The change of CR and CA at 3-month intervals.

| | No. of cases | T group | P | No. of cases | V group | p |
|---|---|---|---|---|---|---|
| ΔCR (3M-0M) | 105 | 14.88 ± 13.06 | **<0.001** | 105 | 2.67 ± 9.49 | **0.005** |
| ΔCR (6M-3M) | 70 | 2.58 ± 3.98 | **<0.001** | 56 | 1.96 ± 3.53 | **<0.001** |
| ΔCR (last-6M) | 33 | 0.10 ± 0.24 | 0.866 | 33 | 0.10 ± 0.51 | 0.293 |
| ΔCA (3M-0M) | 105 | 3.66 ± 3.89 | **<0.001** | 105 | 2.69 ± 5.05 | **<0.001** |
| ΔCA (6M-3M) | 70 | 0.90 ± 2.51 | **0.004** | 56 | 0.46 ± 2.30 | 0.149 |
| ΔCA (last-6M) | 33 | 0.24 ± 1.19 | 0.261 | 33 | −0.01 ± 0.65 | 0.935 |

The bold font indicates a statistical significance ($p < .05$). ΔCR denotes the change of compression rate between follow-up periods, and ΔCA the change of Cobb's angle between follow-up periods.

**Table 3**
The comparison of radiologic and clinical results between two groups.

| | T group | V group | p |
|---|---|---|---|
| No. of cases on 3M | 105 | 105 | |
| CR 0M (%) | 25.51 ± 15.81 | 29.48 ± 15.63 | 0.069 |
| CR 3M (%) | 40.39 ± 19.77 | 32.15 ± 15.60 | **<0.001** |
| ΔCR (3M-0M) (%) | 14.88 ± 13.06 | 2.67 ± 9.49 | **<0.001** |
| CR > 10% 3M (%) | 58.1 | 17.1 | **<0.001** |
| CR > 15% 3M (%) | 41.0 | 10.5 | **<0.001** |
| CR > 20% 3M (%) | 32.4 | 5.7 | **<0.001** |
| CA 0M (°) | −2.01 ± 15.62 | 2.45 ± 14.72 | **0.035** |
| CA 3M (°) | 1.65 ± 16.78 | 5.14 ± 15.47 | 0.119 |
| ΔCA (3M-0M) (°) | 3.66 ± 3.89 | 2.69 ± 5.05 | 0.121 |
| CA > 5° 3M (%) | 36.2 | 16.2 | **<0.001** |
| CA > 10° 3M (%) | 10.5 | 3.8 | 0.061 |
| CA > 15° 3M (%) | 1.9 | 0 | 0.498 |
| POB 3M (%) | 18.1 | 7.6 | **0.023** |
| Union 3M (%) | 65.7 | 91.4 | **<0.001** |
| Outcome 3M (success, %) | 77.1 | 94.3 | **<0.001** |
| Cement leakage (%) | 0 | 45.7 | |
| Epidural | 0 | 12.4 | |
| Paravertebral | 0 | 12.4 | |
| Intradiscal | 0 | 31.4 | |
| Refracture (%) | 12.4 | 4.8 | **0.048** |
| No. of cases on 6M | 70 | 56 | |
| CR 6M (%) | 45.72 ± 20.88 | 36.24 ± 16.14 | **0.005** |
| ΔCR (6M-3M) | 2.58 ± 3.98 | 1.96 ± 3.53 | 0.293 |
| CA 6M (°) | 4.14 ± 17.82 | 5.29 ± 15.45 | 0.708 |
| ΔCA (6M-3M) | 0.90 ± 2.51 | 0.46 ± 2.30 | **0.017** |
| POB 6M (%) | 28.2 | 8.9 | **0.007** |
| Union 6M (%) | 88.6 | 100 | **0.008** |
| Outcome 6M (success, %) | 78.6 | 100 | **<0.001** |
| No. of cases on last F/U | 33 | 32 | |
| CR last F/U (%) | 48.94 ± 20.21 | 35.91 ± 16.83 | **0.006** |
| CA last F/U (°) | 2.91 ± 19.57 | 3.87 ± 15.52 | 0.829 |
| No. of cases on last F/U | 105 | 105 | |
| Last F/U period (months) | 17.0 ± 19.03 | 9.5 ± 10.20 | **<0.001** |
| Subsequent fracture (%) | 10.5 | 12.4 | 0.664 |
| Adjacent | 2.9 | 6.7 | 0.195 |
| non-adjacent | 7.6 | 8.6 | 0.800 |

The bold font indicates a statistical significance ($p < .05$). ΔCR denotes the change of compression rate between follow-up periods, ΔCA the change of Cobb's angle between follow-up periods, and POB paravertebral osseous bridge. Refracture was defined as >15% decrease in body height and 8° decrease in kyphotic angle.

T group than that in the V group at 3 and 6 months. The T-group showed a lower union (66% vs. 91%) and a lower success rate (77% vs. 94%) at 3 months. The two variables demonstrated different patterns at 6 months. Union (89% vs. 100%) improved, but there was no further improvement in the outcome (79% vs. 100%).

### 3.5. Cement leakage, refracture, and subsequent fracture

The occurrence of cement leakage (epidural, paravertebral, and intradiscal) and the incidence of refracture and subsequent fracture (adjacent vs. non-adjacent) at the last follow-up were evaluated (Table 3). In the V group, leakages were detected in 45.7% of cases. Intradiscal leakage (31.4%) was observed. Clinically insignificant epidural leakages occurred in 12.4% of the cases. However, no decompressive surgery was performed. One patient with intercostal pain due to paravertebral leakage causing foraminal stenosis improved with pain intervention only. A higher incidence of re-fracture was observed in the T group (12% vs. 5%, P = .048) at 3 months. This finding supports the superiority of combination treatment. Most subsequent fractures occurred within 6 months, but there was no difference in the occurrence of subsequent fractures between the two groups. Additionally, intradiscal leakage was not associated with adjacent compression fractures.

### 3.6. Age-related subgroup analysis

The older (>65 years) age group treated with TPTD with subsequent VP showed a significant protective effect in ΔCR (3M–0M) and ΔCA>5°. In the oldest (>75 years) group, TPTD with subsequent VP showed the most prominent difference in union and successful outcome. The same pattern was observed at 6 months (Table 4).

### 3.7. Prognostic factors of nonunion

In the univariate analysis of the T group, nonunion was significantly related to the presence of hypertension, thoracolumbar junction level, biconcave and crush type, high fracture grade, presence of fracture gap, presence of IVVC, presence of PVWF, severe CR, and kyphotic CA (Table 5). In the multivariate analysis, hypertension (Exp(B) 3.514, 95% CI 1.452–8.638, P = .0054) and the presence of a fracture gap (Exp(B) 3.456, 95% CI 1.392–8.586, P = .0075) were significant risk factors for nonunion.

In the univariate analysis of the V group, nonunion was more susceptible to biconcave and crush type, large bone marrow signal change on T1WI, presence of fracture gap, and presence of PVWF (Table 5). A multivariate analysis was not performed because of the small number (n = 9) of nonunion cases.

### 3.8. Prognostic factors of failure outcome

In the T group, unfavorable outcomes were significantly related to biconcave and crush type, high fracture grade, presence of IVVC, PVWF, and severe CR in the univariate analysis (Table 6). In the multivariate analysis, IVVC (Exp (B) 8.454, 95% CI 1.026–69.681, P = .047) was the sole risk factor.

For the V group, failure outcome had a significant relationship with biconcave and crush type, high fracture grade, presence of fracture gap, and PVWF. A multivariate analysis was not performed owing to the small sample size (n = 6) of failure cases.

**Table 4**
Age subgroup analysis: the comparison of radiologic and clinical results between two groups.

| | <65 yrs | | | 65–75 yrs | | | >75 yrs | | |
|---|---|---|---|---|---|---|---|---|---|
| | T group | V group | P | T group | V group | p | T group | V group | p |
| No. of cases on 3M | 42 | 11 | | 39 | 25 | | 24 | 69 | |
| CR 0M (%) | 23.14 ± 14.09 | 37.31 ± 17.57 | **0.007** | 26.09 ± 17.77 | 29.02 ± 17.09 | 0.516 | 28.71 ± 15.28 | 28.40 ± 14.64 | 0.930 |
| CR 3M (%) | 36.85 ± 20.27 | 42.85 ± 11.88 | 0.354 | 42.90 ± 21.14 | 32.16 ± 16.66 | **0.036** | 42.50 ± 16.07 | 30.44 ± 15.25 | **0.001** |
| ΔCR (3M-0M) (%) | 13.71 ± 12.40 | 5.53 ± 9.12 | **0.047** | 16.80 ± 13.88 | 3.14 ± 8.88 | **0.000** | 13.68 ± 13.00 | 2.04 ± 9.80 | **0.000** |
| CR > 10% 3M (%) | 50 | 36.3 | 0.420 | 66.7 | 8 | **0.000** | 58.3 | 17.4 | **0.000** |
| CR > 15% 3M (%) | 35.7 | 27.3 | 0.730 | 51.3 | 8 | **0.000** | 33.3 | 8.7 | **0.007** |
| CR > 20% 3M (%) | 31.0 | 0 | **0.047** | 38.5 | 8 | **0.007** | 25 | 5.8 | **0.017** |
| CA 0M (°) | −4.39 ± 15.69 | 3.17 ± 22.58 | 0.202 | 1.05 ± 14.58 | 6.86 ± 10.52 | 0.090 | −2.81 ± 16.93 | 0.73 ± 14.40 | 0.324 |
| CA 3M (°) | −0.61 ± 17.53 | 6.01 ± 23.24 | 0.303 | 4.54 ± 15.82 | 9.84 ± 10.16 | 0.108 | 0.92 ± 16.98 | 3.29 ± 15.44 | 0.529 |
| ΔCA (3M-0M) (°) | 3.77 ± 4.14 | 2.84 ± 2.22 | 0.474 | 3.49 ± 3.60 | 2.98 ± 4.00 | 0.600 | 3.73 ± 4.05 | 2.56 ± 5.71 | 0.358 |
| CA > 5° 3M (%) | 33.3 | 18.2 | 0.471 | 38.5 | 20 | 0.120 | 37.5 | 14.5 | **0.036** |
| CA > 10° 3M (%) | 16.7 | 0 | 0.322 | 5.13 | 8 | 0.640 | 8.3 | 2.9 | 0.273 |
| CA > 15° 3M (%) | 0 | 0 | NA | 0 | 0 | NA | 8.3 | 0 | 0.065 |
| POB 3M (%) | 16.7 | 27.3 | 0.416 | 23.1 | 4 | 0.074 | 12.5 | 5.8 | 0.369 |
| Union 3M (%) | 73.8 | 100 | 0.094 | 61.5 | 92 | **0.007** | 58.3 | 89.9 | **0.001** |
| Outcome 3M (success, %) | 78.6 | 100 | 0.177 | 82.1 | 92 | 0.463 | 66.7 | 94.2 | **0.002** |
| No. of cases on 6M | 27 | 8 | | 27 | 14 | | 16 | 34 | |
| CR 6M (%) | 41.42 ± 22.00 | 42.02 ± 11.54 | 0.942 | 48.18 ± 21.00 | 36.87 ± 18.41 | 0.097 | 48.81 ± 18.63 | 34.63 ± 16.18 | **0.008** |
| ΔCR (6M-3M) | 1.32 ± 2.10 | 0.51 ± 2.47 | 0.360 | 3.23 ± 3.94 | 4.35 ± 4.74 | 0.433 | 3.60 ± 5.79 | 1.41 ± 2.88 | 0.170 |
| CA 6M (°) | 1.19 ± 18.15 | 0.73 ± 24.15 | 0.954 | 8.07 ± 16.91 | 11.62 ± 11.62 | 0.486 | 2.52 ± 18.63 | 3.66 ± 13.92 | 0.811 |
| ΔCA (6M-3M) | 1.13 ± 1.51 | 0.12 ± 2.51 | 0.197 | 1.15 ± 3.53 | 1.28 ± 3.06 | 0.907 | 0.09 ± 1.55 | 0.11 ± 2.11 | 0.977 |
| POB 6M (%) | 29.6 | 12.5 | 0.648 | 33.3 | 14.3 | 0.275 | 18.8 | 5.9 | 0.311 |
| Union 6M (%) | 92.6 | 100 | >0.999 | 88.9 | 100 | 0.539 | 81.3 | 100 | **0.029** |
| Outcome 6M (success, %) | 77.8 | 100 | 0.299 | 81.5 | 100 | 0.147 | 75 | 100 | **0.008** |

The bold font indicates a statistical significance ($p < .05$). ΔCR denotes the change of compression rate between follow-up periods, ΔCA the change of Cobb's angle between follow-up periods, and POB paravertebral osseous bridge.

**Table 5**
The univariate analysis of risk factors regarding the radiologic union.

| Status of the union on 3M | T group | | | V group | | |
|---|---|---|---|---|---|---|
| | Nonunion | Union | p | Nonunion | Union | p |
| No. of cases, (%) | 36 (34) | 69 (66) | | 9 (9) | 96 (91) | |
| Sex (M:F) | 15:21 | 20:49 | 0.191 | 3:6 | 22:74 | 0.483 |
| Age (yr) | 68.89 ± 10.34 | 65.56 ± 10.55 | 0.124 | 80.22 ± 6.46 | 75.91 ± 10.43 | 0.227 |
| Bwt (kg) | 58.31 ± 9.27 | 56.77 ± 7.79 | 0.372 | 58.41 ± 11.72 | 57.08 ± 11.24 | 0.735 |
| Ht (cm) | 158.92 ± 7.46 | 156.57 ± 8.64 | 0.169 | 158.49 ± 10.61 | 155.47 ± 8.19 | 0.305 |
| BMI (kg/m2) | 23.05 ± 3.08 | 23.14 ± 2.52 | 0.866 | 23.22 ± 3.74 | 23.58 ± 3.96 | 0.796 |
| T score | −2.65 ± 1.07 | −2.77 ± 1.26 | 0.637 | −2.94 ± 1.75 | −3.16 ± 1.14 | 0.603 |
| DM (%) | 22.2 | 13.0 | 0.226 | 33.3 | 20.8 | 0.407 |
| HTN (%) | 61.1 | 34.8 | **0.010** | 55.6 | 57.3 | 1.000 |
| hyperlipidemia (%) | 2.8 | 7.2 | 0.662 | 11.1 | 24.0 | 0.681 |
| CKD (%) | 2.8 | 0.0 | 0.343 | 11.1 | 2.1 | 0.238 |
| Steroid Mx (%) | 2.8 | 1.4 | 1.000 | 0 | 2.1 | 1.000 |
| 25-OH vit D (ng/ml) | 20.47 ± 10.53 | 18.28 ± 12.34 | 0.463 | 20.73 ± 10.11 | 18.23 ± 10.20 | 0.485 |
| onset (days) | 5.78 ± 11.58 | 6.12 ± 9.92 | 0.876 | 7.44 ± 6.77 | 10.60 ± 16.37 | 0.568 |
| onset (acute/subacute/chronic) | 31/3/2 | 58/7/4 | 0.834 | 7/2/0 | 68/15/13 | 0.403 |
| Location (T/TL/L) | 2/29/5 | 8/40/21 | 0.368 | 0/9/0 | 11/65/20 | 0.618 |
| Location (TL/others) | 29/7 | 40/29 | **0.021** | 9/0 | 65/31 | 0.055 |
| Type (insufficiency/wedge/biconcave/crush) | 1/17/2/16 | 3/51/2/13 | **0.004** | 0/1/2/6 | 3/59/6/28 | **0.005** |
| Fracture grade (0/0.5/1/2/3) | 1/9/5/12/9 | 1/29/15/18/6 | **0.012** | 0/2/0/3/4 | 0/29/12/31/24 | 0.201 |
| T1 bone marrow signal change (T1BM,%) | 57.86 ± 20.10 | 52.72 ± 22.45 | 0.207 | 78.67 ± 18.49 | 63.30 ± 20.00 | **0.029** |
| Fracture Gap (%) | 50 | 26.1 | **0.014** | 88.9 | 54.2 | 0.075 |
| Fracture Gap (none/small/large) | 18/11/7 | 51/11/7 | **0.025** | 1/2/6 | 44/30/22 | **0.006** |
| IVVC (Y/N) | 7/29 | 0/69 | **<0.001** | 2/9 | 11/96 | 0.308 |
| Posterior vertebral wall fracture (Y/N) | 15/21 | 14/55 | **0.020** | 8/9 | 26/96 | **<0.001** |
| CR 0M (%) | 32.05 ± 18.37 | 22.10 ± 13.20 | **0.006** | 36.05 ± 13.29 | 28.87 ± 15.76 | 0.189 |
| CA 0M (°) | 2.72 ± 12.66 | −4.48 ± 16.52 | **0.007** | 6.56 ± 11.85 | 2.06 ± 14.96 | 0.384 |

The bold font indicates a statistical significance ($p < .05$). M denotes male, F female, Bwt body weight, Ht height, BMI body mass index, DM diabetes mellitus, HTN hypertension, CKD chronic kidney disease, Mx medication, T thoracic, TL thoracolumbar, L lumbar, vHt vertebral height, CR compression rate, CA Cobb's angle, and IVVC intravertebral vacuum cleft.

### 3.9. Case illustrations

Fig. 3 Case with solid union and successful outcome in the T group.
Fig. 4 Cases with nonunion and unfavorable outcome in the T group.
Fig. 5 Case with incomplete union and unfavorable outcome in the T group.
Fig. 6 Cases with solid union and successful outcome in the V group.
Fig. 7 Asymptomatic collapse after vertebroplasty.

**Table 6**
The univariate analysis of risk factors regarding the clinical outcome.

| Clinical outcome on 3M | T group | | | V group | | |
|---|---|---|---|---|---|---|
| | Failure | Success | p | Failure | Success | p |
| No. of cases, (%) | 24 (23) | 81 (77) | | 6 (5) | 99 (95) | |
| Sex (M:F) | 8/16 | 27/54 | 1.000 | 1/5 | 24/75 | 1.000 |
| Age (years) | 68.29 ± 11.14 | 66.22 ± 10.40 | 0.401 | 76.50 ± 3.62 | 76.26 ± 10.47 | 0.898 |
| Bwt (kg) | 57.55 ± 9.75 | 57.22 ± 7.91 | 0.869 | 57.62 ± 13.32 | 57.17 ± 11.17 | 0.925 |
| Ht (cm) | 158.20 ± 8.57 | 157.13 ± 8.25 | 0.582 | 155.23 ± 8.49 | 155.76 ± 8.45 | 0.883 |
| BMI (kg/m2) | 22.89 ± 2.66 | 23.17 ± 2.74 | 0.656 | 23.68 ± 3.56 | 23.54 ± 3.96 | 0.931 |
| T score | −2.85 ± 0.95 | −2.69 ± 1.26 | 0.555 | −2.80 ± 1.56 | −3.16 ± 1.17 | 0.470 |
| DM (%) | 29.2 | 12.3 | 0.062 | 50.0 | 20.2 | 0.118 |
| HTN (%) | 54.2 | 40.7 | 0.244 | 66.7 | 56.6 | 0.698 |
| hyperlipidemia (%) | 4.2 | 6.2 | 1.000 | 16.7 | 23.2 | 1.000 |
| CKD (%) | 0.0 | 1.2 | 1.000 | 16.7 | 2.0 | 0.163 |
| Steroid Mx (%) | 4.2 | 1.2 | 0.407 | 0 | 2.0 | 1.000 |
| 25-OH vit D (ng/ml) | 20.48 ± 10.46 | 18.50 ± 12.20 | 0.545 | 21.96 ± 9.25 | 18.23 ± 10.22 | 0.386 |
| onset (days) | 3.67 ± 6.06 | 6.69 ± 11.39 | 0.215 | 6.67 ± 8.33 | 10.56 ± 16.12 | 0.560 |
| onset (acute/subacute/chronic) | 21/3/0 | 68/7/6 | 0.375 | 4/2/0 | 71/15/13 | 0.785 |
| Location (T/TL/L) | 2/19/3 | 8/50/23 | 0.277 | 0/6/0 | 11/68/20 | 0.688 |
| Location (TL/others, %) | 79.2 | 61.7 | 0.114 | 100 | 68.7 | 0.176 |
| Type (insufficiency/wedge/biconcave/crush) | 1/8/1/14 | 3/60/3/15 | **<0.001** | 0/0/1/5 | 3/60/7/29 | **0.003** |
| Fracture grade (0/0.5/1/2/3) | 1/7/1/8/7 | 1/31/19/22/8 | **0.029** | 0/0/0/3/3 | 0/31/12/31/25 | **0.043** |
| T1 bone marrow signal change (T1BM,%) | 53.58 ± 20.92 | 54.27 ± 22.33 | 0.893 | 75.67 ± 20.72 | 63.95 ± 20.15 | 0.170 |
| Fracture Gap (%) | 41.7 | 32.1 | 0.386 | 100 | 54.5 | **0.036** |
| Fracture Gap (none/small/large) | 14/5/5 | 55/17/9 | 0.250 | 0/2/4 | 45/30/24 | **0.011** |
| IVVC (%) | 16.7 | 3.7 | **0.046** | 33.3 | 11.1 | 0.160 |
| Posterior wall fracture (%) | 50.0 | 21.0 | **0.005** | 83.3 | 29.3 | **0.013** |
| CR 0M (%) | 32.52 ± 19.26 | 23.43 ± 14.12 | **0.006** | 39.52 ± 7.64 | 28.87 ± 15.81 | 0.106 |
| CA 0M (°) | 2.77 ± 13.25 | −3.42 ± 16.06 | 0.088 | 9.43 ± 7.61 | 2.02 ± 14.96 | 0.233 |

The asterisk indicates a statistical significance ($p < .05$). M denotes male, F female, Bwt body weight, Ht height, BMI body mass index, DM diabetes mellitus, HTN hypertension, CKD chronic kidney disease, Mx medication, T thoracic, TL thoracolumbar, L lumbar, vHt vertebral height, CR compression rate, CA Cobb's angle, and IVVC intravertebral vacuum cleft.

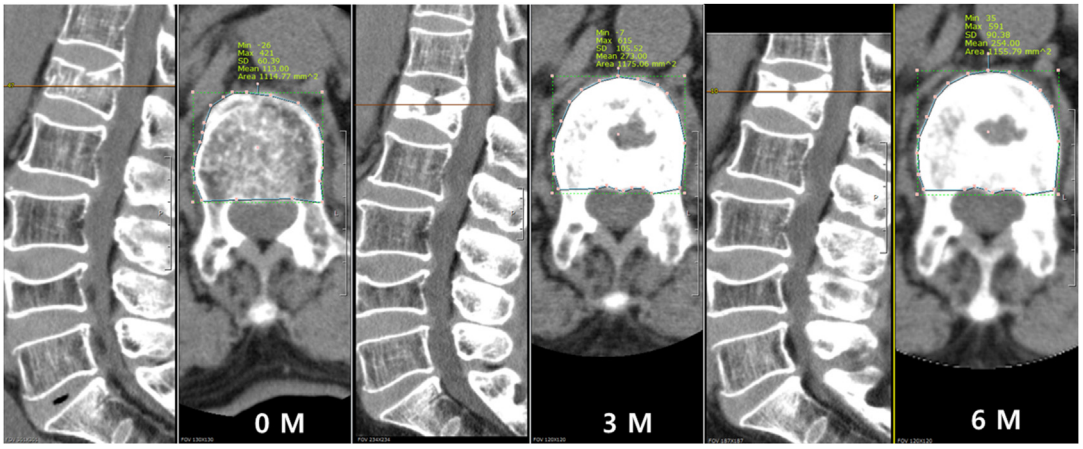



**Fig. 3.** The illustration of case with solid union and successful outcome in the T group. Pretreatment demographic data were as follows: F/74, L1 upper body fracture, wedge type, fracture grade 2, acute onset, T-score −4.9, compression rate 28%, and Cobb's angle 0.5. These serial CT scans were obtained at 0, 3, and 6 months. The solid union was acquired in the bone marrow around the fracture line (Hounsfield values on the corresponding axial images: 113 on admission, 271 at 3 months, 254 at 6 months). The anterior column was maintained. Segmental and regional kyphosis was not aggravated.

## 4. Discussion

In 2009, two NEJM multicenter, randomized, placebo-controlled trials revealed no beneficial effect of VP compared to a sham procedure in patients with painful osteoporotic vertebral fractures. Zou et al[8] insisted that the injection of local anesthetics in the control group might mask the therapeutic effectiveness. Moreover, issues relating to the unreported preexisting kyphosis, simplified compression rate, and different VP techniques in terms of the injected cement volume, volume fraction, and cement distribution with interdigitation pattern should be considered; this remains controversial. From 2010 to 2021, a total of 13 randomized controlled trials of percutaneous VP versus best medical management practices were found in Pubmed.[9–21] Only two trials[15,18] provided further evidence that the use of this treatment in routine care is not supported by long-term follow-up. Other studies support long-term therapeutic effects. In a recent network meta-analysis of 18 trials, percutaneous vertebral augmentation performed better than conservative treatment in alleviating acute, subacute, and chronic osteoporotic vertebral compression fracture pain in the short- and long-term.

The treatment strategy should also be determined to prevent vertebral collapse and enhance the union rate. The author focused on the interactive and synergistic actions occurring at the interface between trabecular bone and cement. With TPTD and subsequent vertebroplasty, bone cement distributed between trabecular bones may deliver

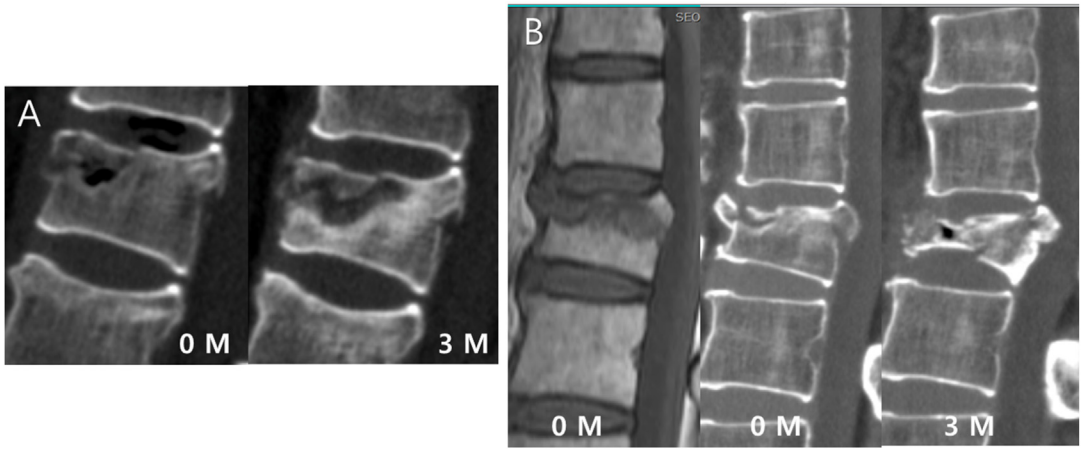



**Fig. 4.** The illustration of case with nonunion and unfavorable outcome in the T group. A, T12 and L1 compression fracture (F/71, T-score −2.6). These serial CT scans demonstrated the trabecular bone around gas formation, which was regarded as intravertebral vacuum cleft, was absorbed. The residual trabecular bed showed the evidence of bone formation. B, In the L1 compression fracture (M/74, T-score −2.3) with posterior vertebral wall fracture, anterior and middle column of vertebral body were collapsed. Gas formation and not prominent trabecular bone formation were observed.

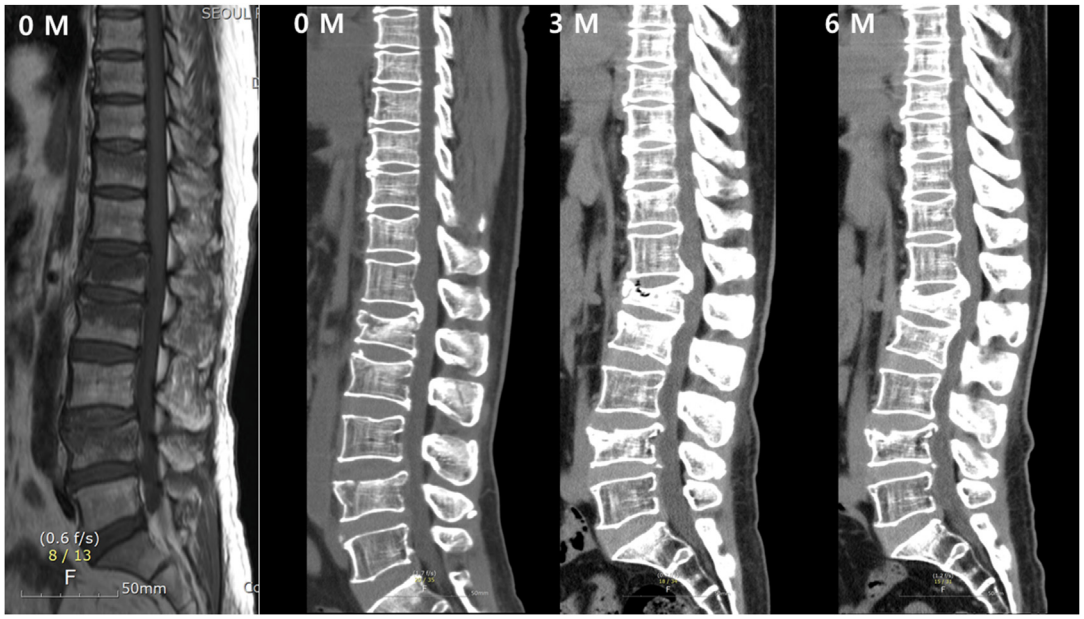



**Fig. 5.** The illustration of case with incomplete union and unfavorable outcome in the T group. Among multiple (T11, L1, L2, L4) compression fractures (F/60, T-score −2.6), L1 fractured body had a fracture gap at 0 month. The collapse in the anterior body accompanied segmental and regional kyphosis at 3 months and the intravertebral vacuum cleft, which mean incomplete union, were also observed. At 6 months, union was completed but back pain persisted around the fractured level.

biomechanical stimuli better, resulting in enhanced bone formation. Therefore, this response must be considered. This is not just about vertebroplasty. TPTD has been shown to enhance callus formation by stimulating the proliferation and differentiation of osteoprogenitor cells. It also increases the production of bone matrix proteins and enhances osteoclastogenesis during the callus remodeling phase. Positive mechanisms for bone healing have been observed in human studies. In a multicenter prospective randomized study by Ebata et al,[22] combining lumbar interbody fusion surgery and TPTD was suggested for managing lumbar degenerative disease in elderly patients. A retrospective cohort study supported the effectiveness of TPTD on pain relief and quality of life in postmenopausal females with osteoporotic vertebral compression fractures.[23]

A retrospective case-matched study comparing the outcomes of cemented vertebrae with TPTD to those without TPTD demonstrated the addition of TPTD to be associated with higher body height and fewer re-fractures than VP alone.[6] The current study compared TPTD with subsequent VP with TPTD therapy without VP and revealed fewer re-fractures in the V group (12%) than in the T group (5%). Ma et al.'s real-world prospective cohort study proved that TPTD-only treatment was not inferior to alendronate with VP treatment.[24] A retrospective study by Yu et al[25] suggested that adding VP to TPTD for osteoporotic thoracolumbar burst fracture in elderly female patients was more helpful in improving structural restoration than TPTD alone. This study supports the findings of previous studies.

Compared to the treatment with optimal pain medication in 30 patients (30 fractures, T/TL/L 3/21/6, M/F 8/22, 68 years, T score −2.9, CR 24% CA 2.2°, unpublished data), an overwhelming increase in ΔCR (29%, compared with 15%(T) and 3%(V)) was identified between 0 and 3-month of follow-up. Cases with a CR>10% (87%, compared with 58%(T) and 18%(V)) were observed. ΔCA (9.2°, compared with 3.7°(T) and 2.5°(V)) was aggravated. Cases with a CA>5° (60%, compared with

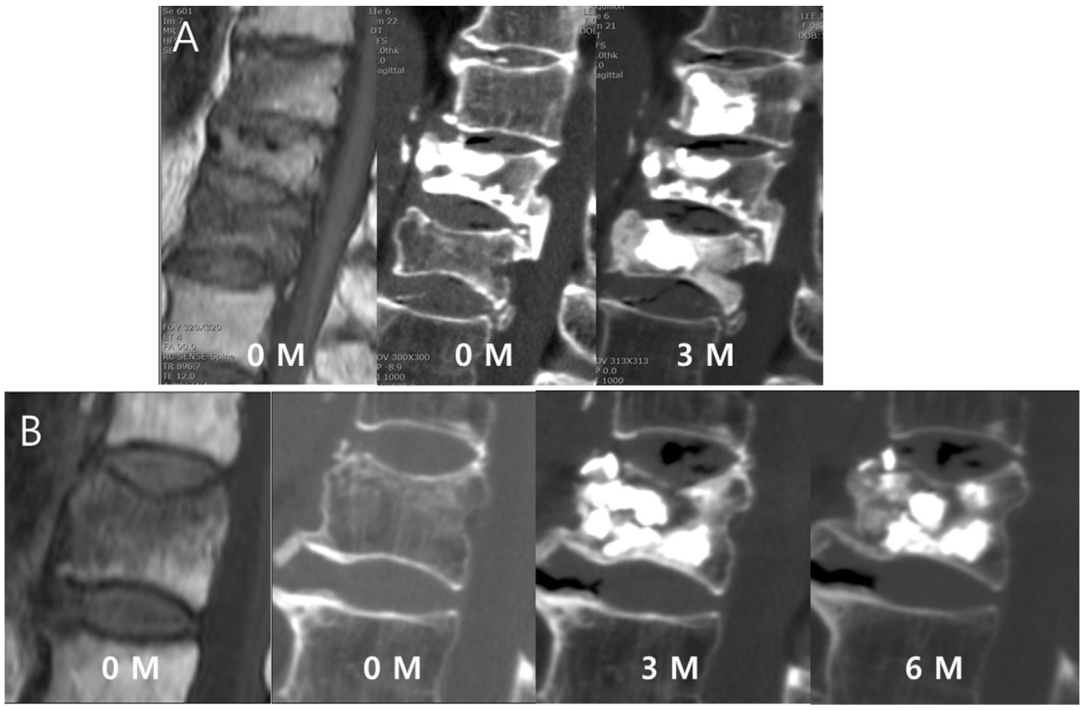



**Fig. 6.** The illustration of cases with solid union and successful outcome in the V group. A, The patient (F/85, T-score −2.8, T11, L1 compression fractures) had the previous history of vertebroplasty. These serial CT scans demonstrated the prominent trabecular bone formation around the injected cement, which means the interactive response by both of teriparatide action and bone cement with interdigitation. Compression rate and Cobb's angle were well maintained at 3 months. B, L1 compression fracture (F/90, T-score −3.8) were collapsed to a minimal degree. But gas formation, which means nonunion, around the cement was not observed at 3 and 6 months.

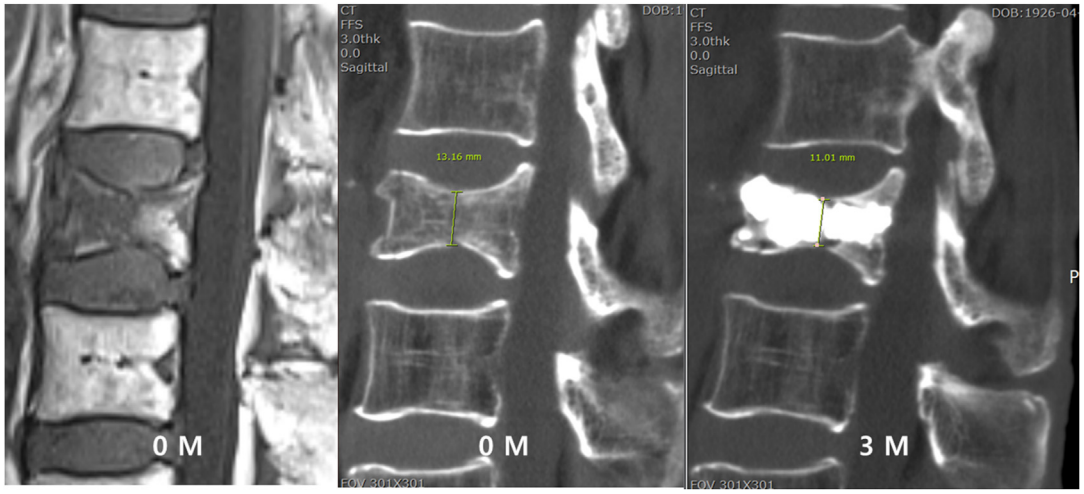



**Fig. 7.** Asymptomatic collapse of L2 compression fracture (M/91, T-score −5.1) was shown while evidences like gas formation or bony erosion around the injected cement of nonunion were not found on CT scan at 3 months. The angulation of kyphosis did not aggravate at all. The patient improved much (VAS 0, no percussion tenderness on the spinous process, and no motion-related provoked back pain).

36%(T) and 14%(V)) were confirmed. The progression of CR and CA is undoubtedly related to the low union rate (40%, compared with 66%(T) and 92%(V)) and low success rate (40%, compared with 77%(T) and 95%(V)).

This distinction may be due to the protection of the vertebral collapse in the earlier period. The global sagittal imbalance accompanied by segmental or regional kyphosis caused by this vertebral collapse plays a crucial role in severe functional disability and pain at the fracture site and paraspinal muscle of the thoracolumbar junction. Therefore, even minimal changes in the CR and CA should not be ignored to maintain or recover the sagittal conformation of the fractured vertebra. The current study demonstrated that TPTD with VP was superior to other treatment modalities in patients with osteoporotic compression fractures. In summary, this strategy should be considered the best option for osteoporotic compression fractures.

The fracture gap surrounded by the fractured cancellous bone may be mostly filled with hematoma (acute phase), callus (subacute phase), or gas (chronic phase in case of a failed union). Bone remodeling may be predominantly initiated. Due to motion, microtrauma of the fractured cancellous bone may increase microfracture and bone resorption of the trabecular bone and preclude bony healing. This situation can be aggravated by daily living activities, such as regular eating, going to the

bathroom, taking a shower, and washing. The trabecular bone around the fracture gap may not obtain sufficient mechanical load to facilitate modeling-based bone formation. The need for a VP arises from this point. In early osteoporotic vertebral compression fractures, augmented cement fills the fracture gap and interdigitates the trabecular bone. It provides a substantial mechanical load and immediate stability to the surrounding trabeculae. It may also help to reduce micromotion and stimulate bone formation in the trabecular bone around the cement. In the T group, fracture gap was a risk factor for nonunion based on multivariate analysis. Since the fracture gap is associated with nonunion caused by micromotion, VP is necessary for the union. In the V group, this finding was no longer found to influence union.

The next role was the anabolic effect of TPTD. Lindsay et al[26] reported that 70% of bone formation by TPTD was based on remodeling, whereas 30% was modeling-based, and modeling was incredibly dominant within the first two months after TPTD induction. These findings are related to high attenuation in the trabecular bone around the cement on a 3-month follow-up CT scan, which indicates bone formation and supports the early treatment of TPTD. In the present study, this hypothesis was proven to be correct. However, the appropriate duration of TPTD remains to be determined. There is an increase in bone formation markers during the first month of treatment, suggesting that bone formation exceeds bone resorption early during the treatment course.[27] After that, bone resorption markers rise. Both bone turnover markers peaked after 6–12 months of TPTD therapy, followed by a gradual decrease.[27] To summarize, TPTD is most likely to stimulate modeling-based bone formation early, followed by remodeling-based bone formation several months later.[27] In terms of the concept of the anabolic window, the period when TPTD is maximally anabolic, six months will be required for the union in the TPTD only treatment according to the results of this study (65.7% at three months vs. 88.6% at six months). Assuming that TPTD with VP treatment (91.4% at three months vs. 100% at six months) is selected, a bare minimum is most likely to be three months to achieve a tolerable union rate and favorable outcome.

POB, also known as new bone formation in the periosteal callus of the fracture healing process,[28] developed in 18.1% of the T group compared to 7.6% of the V group at three months. The compensatory response to spinal instability dominated during that period, but TPTD's anabolic effect is also more likely to influence bony growth (28.2% vs. 8.9% at six months). According to this result, POB may be a meaningful sign of instability within three months.

For the accurate evaluation of CR and CA, a CT scan was selected as a measurement tool because the exact change in height and angle could not be assessed without an accurate true lateral view of the standing X-ray. However, underestimating regional kyphosis compared with global sagittal alignment during the standing posture remains a limitation. In addition, kyphotic angulation is susceptible to varying conditions, such as the location of the fracture, dysfunction of the spinal erector muscle, and sensitivity to fracture-related pain during standing. If all conditions were not adequately considered, individual variation would disturb the exact interpretation of the sagittal alignment changes, including the compressed vertebra and the degeneration of adjacent discs. Therefore, in the present study, a CT scan may have an advantage in that the supine position can lessen individual variation, such as erector spinae dysfunction and pain sensitivity. Therefore, CA results should be regarded as the minimum change.

For accurate evaluation of pain outcomes, the methods were not confined to a visual analog scale. Two findings were checked thoroughly during the physical examinations to rule out other confounding factors, such as preexisting facetogenic and discogenic back pain; one, percussion tenderness on the spinous process of the fractured vertebra, and two, motion-related pain during flexion-extension and standing from sitting. These complicated criteria aimed at discriminating truly improved patients from less-improved patients from the viewpoint of mechanical pain.

IVVC was the only risk factor for failure in the T group in the multivariate analysis. In cases of IVVC, the trabecular bone around osteonecrosis is unlikely to be filled with cement because of low pressure during cement injection (also known as a lump pattern). A lump pattern with less interdigitation may induce microfractures around the cement. Patients with these features mostly had unfavorable outcomes. Nonetheless, VP may reduce the negative effects of IVVC on the outcomes in the V group.

This study had the limitation of inequality in demographic data. Patient willingness should be ruled out to compare the treatment results. However, the current study protocol allowed patients with more pain originating from instability, progressive collapse, and kyphosis to select VP as a salvage procedure. Generally, older patients with compression fractures have severe osteoporosis, which causes more pain, collapse, and kyphosis. Therefore, the mean age of the V group was higher than that of the T group. Surprisingly, the V group exhibited superior results. A matched study is needed with more cases in the T group. This shortcoming cannot be controlled by propensity score matching or 1–1 matching. Matching has the limitation of losing too many patients due to the same sample size in both groups and the stark differences between the groups. Both propensity score matching and exact matching matched less than 50% of the patients, considering the main variables. Logistic regression analysis was performed with the V group as the dependent variable to estimate a propensity score, and model discrimination was assessed with c statistics (=0.894), suggesting that baseline characteristics could determine both groups. In addition, even after matching, a significant number of variables in both groups showed a standardized mean difference (SMD) $> 0.2$. The author decided it would be better to conduct a subgroup analysis rather than to use a small data volume after matching. Accordingly, subgroup analysis according to age was performed. The present protocol of TPTD with VP may be more helpful for the selected age (>75 years) group.

## 5. Conclusion

TPTD with VP was superior to other treatment strategies in patients with osteoporotic compression fractures. This treatment may prevent the aggravation of compression and the progression of kyphotic angulation in the earlier period and may also guarantee a high union rate and favorable outcome.

## Credit author statement

Yongjun Jin: Conceptualization, Methodology, Software Data curation, Writing- Original draft preparation, Visualization, Investigation, Supervision. Writing- Reviewing and Editing

## Funding resources

Nothing to disclose.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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