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ORIGINAL ARTICLE

Can antiosteoporotic therapy reduce mortality in MRI-proved acute osteoporotic vertebral fractures?

Ying-Chou Chen[1] · Fu-Mei Su[1] · Tien-Tsai Cheng[1] · Wei-Che Lin[2] · Chun-Chung Lui[2]

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Abstract Patients with MRI-proved acute painful vertebral fractures in whom conservative pain management fails are frequently referred for vertebroplasty. This study investigated the effects of treating osteoporosis on the mortality rate of patients with MRI-proved acute osteoporosis-related vertebral fractures who had undergone vertebroplasty. We retrospectively reviewed the cases of osteoporosis patients with MRI-proved acute vertebral fractures who had been treated with vertebroplasty from January 2001 to December 2007. The long-term outcomes of the patients who received antiosteoporotic therapy were compared with those of patients who received no therapy. A total of 304 patients (247 female patients and 57 male patients; mean age, 74.1 ± 7.7 years) were enrolled in the study. The patients who received antiosteoporotic therapy had a significantly lower mortality rate than did patients who did not receive antiosteoporotic therapy ($P = 0.001$; hazard ratio, 0.396, 95 % confidence interval, 0.273–0.575). At the end of the study, 183 patients were alive, and 121 had died. Effective treatment for osteoporosis may improve survival in patients with osteoporosis-related vertebral fractures after vertebroplasty.

✉ Ying-Chou Chen
r820713@ms13.hinet.net

[1] Department of Rheumatology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan, 123 Ta-Pei Road, Niao-Sung District, Kaohsiung 833, Taiwan

[2] Department of Radiology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, 123 Ta-Pei Road, Niao-Sung District, Kaohsiung 833, Taiwan

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Introduction

Osteoporotic fractures of the spine are common with aging, and the lifetime risk of a symptomatic vertebral compression fracture has been estimated to be 18 % for women and 11 % for men [1]. In addition, painful, clinically apparent vertebral fractures have been reported to increase overall mortality by up to 15 % [2]. Furthermore, some individuals will become disabled by severe pain that lasts longer than 2–3 months.

Patients with acute painful vertebral fractures who fail to achieve relief with conservative pain management are frequently referred for vertebral augmentation procedures [3]. Vertebroplasty has been used for more than a decade; however, despite favorable clinical outcomes that might be presumed to confer a survival advantage, there are few studies on mortality among patients who undergo this procedure [4, 5].

Antiosteoporotic therapy increases spinal, total hip, and femoral neck bone mineral density. Results from recent studies of patients who have received antiosteoporotic treatment have increasingly shown reductions in the incidence of vertebral fractures [6]. Data from studies of pharmacologic agents used to reduce the risk of fractures provide a way to test the hypothesis that treating osteoporosis reduces the risk of death. If treating osteoporosis does have a positive impact on mortality among patients who have undergone vertebroplasty, there would be several important potential implications for managing skeletal health specifically, and implications for health care of the elderly in general. Thus, in this study, we investigated whether treatment of osteoporosis affects mortality rates in patients who have undergone vertebroplasty.

Materials and methods

The study design was a retrospective review of cases of osteoporosis patients with acute vertebral fractures proved by MRI with low signal intensity (SI) on T1-weighted imaging, enhanced SI on T2-weighted imaging, and enhanced fat-suppressed SI on T1-weighted imaging of the injured vertebral body [7]. All patients in the study had been treated with vertebroplasty at Kaohsiung Chang Gang Memorial Hospital between January 2001 and December 2007. Institutional review boards from Kaohsiung Chang Gang Memorial Hospital provided ethical approval, and the study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice Guidelines. In accord with Taiwanese law, no additional informed consent was required. Patient information was anonymized and de-identified before data analysis.

The inclusion criteria were an MRI diagnosis of acute vertebral fracture: low SI on T1-weighted imaging, enhanced SI on T2-weighted imaging, and enhanced fat-suppressed SI on T1-weighted imaging of the injured vertebral body among patients who had undergone vertebroplasty for a painful vertebral compression fracture. We obtained the electronic medical records of all patients who underwent vertebral augmentation procedures. Patients were excluded if their fracture had a pathologic source or had been caused by more than minimal trauma.

Follow-up for each participant was calculated as the time from inclusion in the study to December 31, 2013, or the time of death, whichever occurred first. All patients included in the study underwent baseline bone density studies, and age, gender, and body mass index (kg/m^2) were recorded. All associated medical diseases, such as diabetes, hypertension, and liver and renal disease, were recorded. Use of any of the following antiosteoporotic drugs was also recorded: alendronate, raloxifen, calcitonin, and teriparatide.

Statistical analysis was performed using SPSS version 21.0 (SPSS, Chicago, IL, USA). Kaplan-Meyer analysis with the log-rank test was performed for different groups of antiosteoporotic agents. Comparisons between independent means were analyzed using the independent *t* test. Relationships between categorical variables were evaluated with the chi square test. Cox regression analysis was used to make adjustments for potential confounding factors. $P < 0.05$ was considered to be statistically significant.

Results

Three hundred four patients with MRI-proved acute vertebral fractures (Fig. 1) who underwent vertebroplasty between January 2003 and December 2007 were enrolled in this study; 64 % were women. The mean age at the index day was 72.21 ± 9.68 years for men and 74.52 ± 7.13 years for women. The mean follow-up period was 7.08 ± 3.67 years. All were grade 3 on the semiquantitative grading scale for vertebral fracture and had T-score < −2.5 measured by bone densitometry.

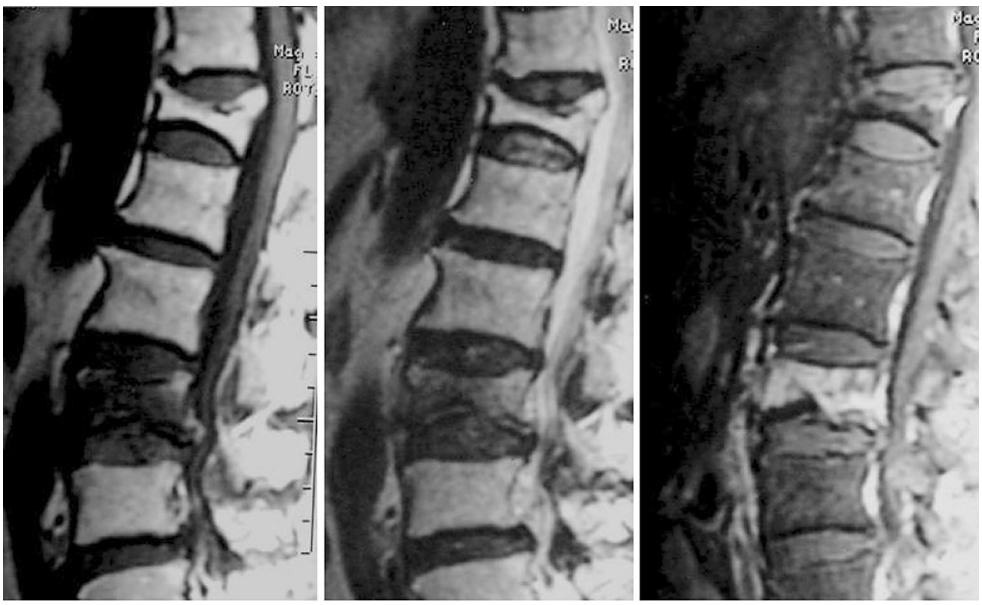

Fig. 1 Acute vertebral fracture was confirmed by MRI with low signal intensity on T1-weighted imaging (*T1W*), enhanced signal intensity on T2-weighted imaging (*T2W*), and contrast enhancement (*C+*)

At the end of the follow-up period, 183 of the original 304 patients had survived, and 121 patients had died. The mean age of those who died was 74.97 ± 7.778 years, compared with 73.19 ± 8.180 years for those who were still alive. There were no significant differences in gender, body mass index, number of vertebral fractures, previous hip fracture, alcohol consumption, or underlying diseases, including diabetes, hypertension, cardiovascular disease, pulmonary disease, liver disease, kidney disease, or neurological disease. In contrast, smoking ($P = 0.045$) increased mortality, and antiosteoporotic therapy decreased mortality ($P = 0001$), and incidence of subsequent fractures (spine, hip, and forearm) was lower in the alive group (Table 1).

One hundred seventy-eight patients accepted antiosteoporotic therapy after vertebroplasty: alendroante for 84 patients (47.5 %), raloxifen for 46 patients (26 %), calcitonin for 34 patients (19.2 %), and teriparatide for 13 patients (7.3 %). Overall, the adherence rate ws 70.4 %.

Antiosteoporotic therapy after vertebroplasty had a significant effect on survival, according to the Kaplan–Meier curve (Fig. 2). When we made adjustments for potential confounding factors such as smoking, alcohol consumption, diabetes, hypertension, cardiovascular disease, pulmonary disease, liver disease, kidney disease, and neurological disease, the treated patients still had a lower mortality rate than those who did not receive treatment ($P = 0.001$; hazard ratio, 2.585, 95 % confidence interval, 1.781–3.754). Whereas mortality increased in patients with diabetes ($P = 0.025$; hazard ratio,1.605; 95 % confidence interval, 1.061–2.427), smoking, alcohol consumption, hypertension, cardiovascular disease, pulmonary disease, liver disease, kidney disease, and neurological disease were not associated with an increase in the risk of death ($P > 0.005$) (Table 2). When we evaluated the cause of mortality, we found the commonest cause was infection (pneumonia, septicemia, urinary tract infection), and antiosteoporotic therapy was associated with a lower infection rate (Table 3). There were no differences in the rates of cancer, cardiovascular events, stroke, or renal failure.

Table 1 Characteristics of study patients who died and those who survived

Variable	Died ($n = 121$)	Alive ($n = 183$)	P
Age (years)	74.97 ± 7.778	73.19 ± 8.180	0.105
Body mass index (kg/m^2)	22.667 ± 5.2129	23.352 ± 4.4020	0.302
Gender			0.549
Female	96 (79.3 %)	151 (82.5 %)	
Male	25 (20.7 %)	32 (17.5 %)	
Spine fracture (number)	1.94 ± 1.157	1.96 ± 1.354	0.935
Previous hip fracture			0.221
Yes	8 (6.6 %)	18 (9.8 %)	
No	113 (93.4 %)	165 (90.2 %)	
Subsequent fracture			0.039
Yes	26 (21.5 %)	24 (13.1 %)	
No	95 (78.5 %)	159 (86.9 %)	
Smoking			0.045
Yes	14 (11.6 %)	9 (4.9 %)	
No	107 (88.4 %)	174 (95.1 %)	
Alcohol consumption			0.122
Yes	7 (5.8 %)	4 (2.2 %)	
No	114 (94.2 %)	179 (97.8 %)	
Diabetes mellitus			0.148
Yes	39 (32.2 %)	44 (24.0 %)	
No	82 (67.8 %)	139 (76.0 %)	
Hypertension			0.557
Yes	67 (55.4 %)	94 (51.4 %)	
No	54 (44.6 %)	89 (48.6 %)	
Neurological disease			0.39
Yes	3 (2.5 %)	2 (1.1 %)	
No	118 (97.5 %)	181 (98.9 %)	
Cardiovascular disease			0.325
Yes	2 (1.7 %)	8 (4.4 %)	
No	119 (98.3 %)	175 (95.6 %)	
Pulmonary disease			0.437
Yes	8 (6.6 %)	8 (4.4 %)	
No	113 (93.4 %)	175 (95.6 %)	
Liver disease			0.353
Yes	10 (8.3 %)	10 (5.5 %)	
No	111 (91.7 %)	173 (94.5 %)	
Kidney disease			0.657
Yes	1 (0.8 %)	2 (1.1 %)	
No	120 (99.2 %)	181 (98.9 %)	
Antiosteoporotic therapy			0.001
Yes	50 (41.3 %)	128 (69.9 %)	
No	71 (58.7 %)	55 (30.1 %)	

Discussion

Established osteoporosis has been associated with a high mortality rate after adjustments for age and comorbidities [8, 9]. Prevalent vertebral deformities have been reported to predict increased mortality and fracture rates in both men and women [10–15]. Treatment of osteoporosis with established efficacy for vertebral and nonvertebral fractures has been reported to reduce mortality in older, frailer individuals who are at a high risk of fractures [6, 16, 17].

Vertebral fractures are the fractures most commonly associated with osteoporosis, and clinically apparent vertebral deformities are associated with poorer survival. Most individuals with radiographically apparent vertebral deformities do not, however, seek medical care [9, 18]. Vertebroplasty is a minimally invasive percutaneous technique for the treatment of symptomatic vertebral body

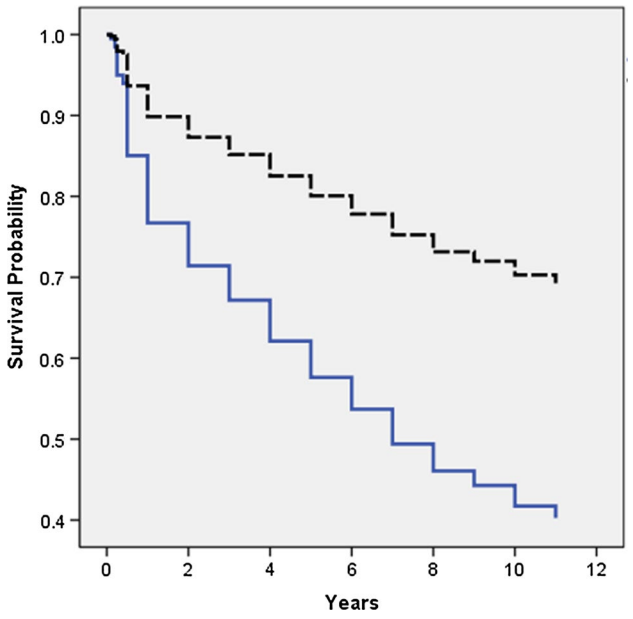

Fig. 2 Comparison of Kaplan–Meier survival for the antiosteoporotic therapy cohort (*dashed line*) and the untreated cohort (*solid line*)

Table 2 Hazard ratios (HR) of antiosteoporotic therapy and mortality after adjustment for other variables

Variable	Regression coefficients	SE	*P*	HR[a]
Antiosteoporotic therapy	−0.925	0.189	0.001	0.396 (0.273–0.575)
Gender	−0.224	0.286	0.435	0.800 (0.456–1.402)
Body mass index (kg/m^2)	−0.003	0.021	0.881	0.997 (0.956–1.039)
Age (years)	0.026	0.013	0.050	1.026 (0.999–1.052)
Smoking	0.421	0.413	0.308	1.524 (0.678–3.426)
Alcohol consumption	0.555	0.506	0.273	1.742 (0.646–4.696)
Diabetes	0.473	0.211	0.025	1.605 (1.061–2.427)
Hypertension	0.108	0.198	0.586	1.114 (0.756–1.641)
Neurological disease	0.638	0.613	0.297	1.893 (0.570–6.291)
Liver disease	0.693	0.348	0.104	1.757 (0.892–3.437)
Kidney disease	−0.152	1.009	0.880	0.859 (0.119–6.201)
Cardiovascular disease	−1.042	0.719	0.147	0.353 (0.086–1.442)
Pulmonary disease	0.256	0.380	0.501	1.292 (0.613–2.723)

SE standard error

[a] The 95 % confidence interval is given in *parentheses*.

fractures caused by osteoporosis, and positive outcomes have been demonstrated in many trials [19, 20]. The advantages include pain relief and restoration of vertebral body height, but there is little evidence of its longer-term safety

Table 3 Causes of death among the two study groups

Cause	Antiosteoporotic therapy ($n = 178$)	Placebo ($n = 126$)	*P*
Cancer			0.746
Yes	5 (2.8 %)	5 (4.0 %)	
No	173 (97.2 %)	121 (96.0 %)	
Cardiovascular disease			0.572
Yes	1 (0.6 %)	2 (1.6 %)	
No	177 (99.4 %)	124 (98.4 %)	
Infection			0.001
Yes	42 (23.6 %)	62 (49.2 %)	
No	136 (76.4 %)	64 (50.8 %)	
Stroke			0.414
Yes	0 (0.0 %)	1 (0.8 %)	
No	178 (100.0 %)	125 (99.2 %)	
Renal failure			0.414
Yes	0 (0.0 %)	1 (0.8 %)	
No	178 (100.0 %)	125 (99.2 %)	

[21–23]. Fractured vertebrae treated with bone cements are stiffer than untreated vertebrae and thus may transfer a greater load to adjacent vertebral levels [24, 25]. Thus, the disadvantage is the concern that these procedures could lead to a heightened rate of subsequent fractures. Vertebroplasty candidates represent the subpopulation of vertebral compression fractures with the highest risk of death owing to associated comorbid conditions and the intrinsic severity of their osteoporotic disease. Patients who do undergo vertebroplasty have been reported to have a mortality rate similar to that of those with untreated symptomatic fractures, but a worse mortality rate compared with those with asymptomatic vertebral fractures [5]. Our patients had high mortality possibly owing to advanced age and long follow-up times.

Specific medical therapy for osteoporosis includes anticatabolic drugs, bisphosphonates, estrogen replacement therapy, and parathyroid hormone analogs. Bisphosphonates are the compounds most commonly used to treat postmenopausal osteoporosis. In our review, alendronate was the drug most commonly used to treat osteoporosis, with an overall adherence rate of 70 %. This may be reason for the relative lower mortality rate.

In one study of mortality and morbidity associated with osteoporosis drug treatment following a hip fracture, mortality was significantly lower in treated patients than in a group that was not treated [8]. The lower mortality rate in the treated group, combined with the knowledge that antiresorptive drugs reduce fractures and increase bone density, merits a randomized trial, and antiresorptive therapy should be considered for all patients after a hip fracture.

In clinical practice, some patients with vertebral fractures receive no medical therapy after vertebroplasty. In our cohort, 178 of the 304 patients (58.6 %) accepted antiosteoporotic therapy. Thus, even among patients with symptomatic vertebral fractures, some patients did not seek further treatment, and this attitude may contribute to subsequent vertebral fractures and increased mortality [26]. Our data show that antiosteoporotic therapy can reduce mortality, underscoring the importance of educating patients with osteoporosis about the value of medical therapy.

Why does antiosteoporotic therapy decrease mortality? A possible pathway is through a drug effect on the immune system. In addition to the changes in the levels of cytokines and the monocyte–macrophage system [27], there is epidemiologic evidence to support this hypothesis. A greater than tenfold increased risk of infectious death, particularly septicemia and pneumonia, was seen in a cohort of hip fracture patients relative to the general population over 2 years [28]. Antiosteoporotic therapy patients were less likely to die of pneumonia.

There are several limitations to this study. First, the sample size was small. Second, because the study had a retrospective design, we could not include complete data, such as the use of vitamin D and calcium supplements. Third, there was a lack of complete bone mineral density data after osteoporosis treatment. However, in this single-center cohort, we collected as many data as possible, and this study included only fragility fractures in patients older than 50 years without a secondary cause. Thus, the patients' fractures were due to osteoporosis.

This study also has a number of strengths. First, it was a long-term cohort study with a mean follow-up period of 7 years, which made it possible to gather sufficient follow-up data on survival. In addition, baseline MRI scans were taken for all participants, all of whom had clinically diagnosed vertebral fractures. Thus, we were able to exclude other secondary causes of vertebral fracture such as cancer or pyogenic infection.

Our results showed that pharmacologic therapy can reduce the mortality rate of patients with osteoporosis and vertebral fractures. After adjustment for comorbidities, the patients who received pharmacologic therapy still had lower mortality rates. Thus, optimal osteoporosis management may reduce the risk of death. The reduction in infection led to decreased mortality in the osteoporosis management group. A possible reason may be that osteoporosis management decreased refracture rates and the improved health-related quality of life and therefore the infection rate was relatively low.

In conclusion, the results of this study show that antiosteoporotic therapy is associated with a decreased risk of death. Thus, after vertebroplasty, aggressive medical therapy is suggested for all patients with osteoporosis.

Conflict of interest Ying-Chou Chen, Wei-Che Lin, Chun-Chung Lui, Fu-Mei Su, and Tien-Tsai Cheng declare that they have no conflict of interest.

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