Osteoporosis International (2019) 30:2249–2256
https://doi.org/10.1007/s00198-019-05125-0

ORIGINAL ARTICLE

Effects of anti-osteoporosis medications on radiological and clinical results after acute osteoporotic spinal fractures: a retrospective analysis of prospectively designed study

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Received: 20 March 2019 / Accepted: 6 August 2019 / Published online: 17 August 2019

Abstract

Summary Effects of anti-osteoporosis medications such as anti-resorptive and anabolic agents on healing of osteoporotic spinal fracture were retrospectively investigated. The use of anabolic agent significantly enhanced fracture healing, reduced progressive collapse, and presented good pain relief. These findings suggest that proper selection of medication could improve initial management of acute osteoporotic spinal fractures (OSFs).

Introduction Although anti-osteoporosis medications have beneficial effects on prevention of osteoporotic spinal fractures (OSFs), few studies have compared effects of medications on fracture healing following OSFs. Therefore, the purpose of this study was to elucidate the effects of different anti-osteoporosis medications on radiological and clinical outcomes after acute OSFs.

Methods A total of 132 patients diagnosed with acute OSFs were enrolled and allocated into three groups [group I ($n = 39$, no anti-osteoporosis medication), group II ($n = 66$, bisphosphonate), and group III ($n = 27$, parathyroid hormone (PTH)]. Radiological parameters including magnetic resonance (MR) classification, occurrence of intravertebral cleft (IVC), and clinical outcomes such as numerical rating scale (NRS) and Oswestry disability index were assessed. Risk analyses for IVC and progressive collapse were done along the related factors and medication type.

Results IVC sign was observed in 30 patients. The rate of IVC sign was lower in group III (7.4%) than that in group I (20.5%) or group II (30.3%), although the difference was not statistically significant. Moreover, the degree of NRS improvement was better in group III than that in group I or group II (5.7 vs. 3.1 vs. 3.5, $p < 0.001$). On multiple regression analysis, mid-portion type fracture in MR classification was a significant risk factor for progressive OSFs. The use of PTH showed significant lower incidences of occurrence of IVC (odds ratio (OR) = 0.160) and increase in height loss (OR = 0.325).

Conclusions Different anti-osteoporosis medications presented different clinical and radiological results after acute OSFs. The use of anabolic agent significantly enhanced fracture healing, reduced progressive collapse, and presented better clinical outcomes. Proper selection of medication might improve initial management of acute OSFs.

Keywords Bisphosphonates · Nonunion · Osteoporosis · Osteoporotic spinal fractures · Teriparatide

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Introduction

Due to increase of the elderly population, osteoporosis and related skeletal problems are also increasing [1]. Osteoporotic spinal fracture (OSF) is one of the frequent skeletal related problems [2]. The use of anti-osteoporosis medications as an active intervention method for osteoporosis has shown efficacies by increasing bone mineral density (BMD) and decreasing the risk of fractures in vast randomized studies [3–6]. However, anti-osteoporosis medication can also have negative effect by excessively suppressing physiologic bone remodeling, causing new problems such as atypical femoral fractures and osteonecrosis of the jaw [7, 8]. Although several clinical studies have shown that anti-osteoporosis medication does not have any clinical or radiological effect on fracture healing [9, 10], many basic studies including animal studies have revealed that such medication could impair fracture healing [11, 12]. Our recent study has also shown possible impairment of fracture healing after OSFs by anti-resorptive medications, suggesting suspension of bisphosphonates (BPs) use during fracture healing period for acute OSFs [13]. Parathyroid hormone (PTH), an anabolic agent, is one of anti-osteoporosis medications. The use of PTH has been on the rise recently [14]. PTH stimulates proliferation and activity of osteoblast and inhibits its apoptosis [15]. The basic mechanism of PTH is different from anti-resorptive agents. Theoretically, PTH might enhance healing in acute stage of fractures. Some studies have shown that PTH can help healing of osteoporotic distal radius and pelvis fractures [16, 17]. Also, PTH had been reported to be effective in reducing back pain compared to other treatments [18–20]. Unfortunately, currently, studies do not have convincing evidence that PTH can enhance healing of OSFs. Thus, the objective of this study was to elucidate differences in radiological and clinical results after using anti-osteoporosis medications such as anti-resorptive and anabolic agents for acute OSFs.

Material and methods

This study was performed through retrospective analysis of the clinical and radiologic data. Approval from institutional review board was obtained (IRB approval No. KC18MESI0546).

Study population and treatment protocol

Patients diagnosed with acute OSFs were enrolled in this study. A confirmative diagnosis was made through clinical clues and radiographic studies. Other pathologic fractures such as those related to malignancies or infections were excluded. A total of 132 patients were enrolled and allocated into three groups: group I ($n = 39$, no anti-osteoporosis medication use), group II ($n = 66$, anti-resorptive BP use), and group III ($n = 27$, daily anabolic PTH use, teriparatide 20 μg) depending on the use of anti-osteoporosis medication during the initial fracture healing period (3 months following diagnosis). Basic clinical data such as age, sex, body mass index (BMI), fracture level, and history of anti-osteoporosis medication use were recorded. Standard conservative treatment in this study included 1 week of bed rest and pain control using non-steroidal anti-inflammatory drugs and muscle relaxants. After this period, tolerable ambulation was permitted with a soft brace.

Assessments and statistical analyses

Radiographic parameters including height and local kyphosis of the index vertebra, magnetic resonance (MR) image classification, BMD, and the presence of intravertebral cleft (IVC; Fig. 1) were recorded by two independent spine fellows using previously reported methods. MR image classification was defined as follows [21]. Type I, the endplate type, was defined when cortical disruption of the vertebral body was noted at the endplate area or anterior cortex adjacent to the endplate was noted on a plain radiograph with confined signal changes on T1-weighted images (T1WI) and T2-weighted images (T2WI) noted around the endplate of the affected vertebra on MRI (Fig. 2). Type II, the mid-portion type, was defined when cortical disruption of the vertebral body was noted at the mid-portion of the vertebral body on a plain radiograph with T1WI and T2WI signal changes noted around the mid-portion of the vertebra (Fig. 3). Definition of impaired fracture healing or assessment method following OSFs has not been established yet. Thus, changes of height of the index vertebra and local kyphosis exceeding mean values of this cohort (height loss, 15%; kyphotic angle, 10°) were considered as indicative of impaired fracture healing following OSFs. The presence of IVC and fracture instability at the index vertebra was also considered as indicative of it. For clinical parameters, pain (numerical rating scale, NRS) and disability due to back pain (Oswestry disability index, ODI) were used.

Differences among three groups were analyzed using one-way analysis of variance (ANOVA) for parametric data and chi-square test for nonparametric data. Linear regression was first performed to determine correlation between factors and clinical and radiographic factors suggestive of impaired fracture healing. Multiple logistic regression analysis was performed to assess the association between a history of anti-osteoporosis medication use and fracture healings following OSFs. Factors with $p < 0.2$ on univariate analysis and clinically significant variables were included in the multivariate analysis. Statistical analysis was conducted using SPSS software (IBM SPSS Statistics, Version 24.0, Armonk, NY, USA). Statistical significance was set at $p < 0.05$.

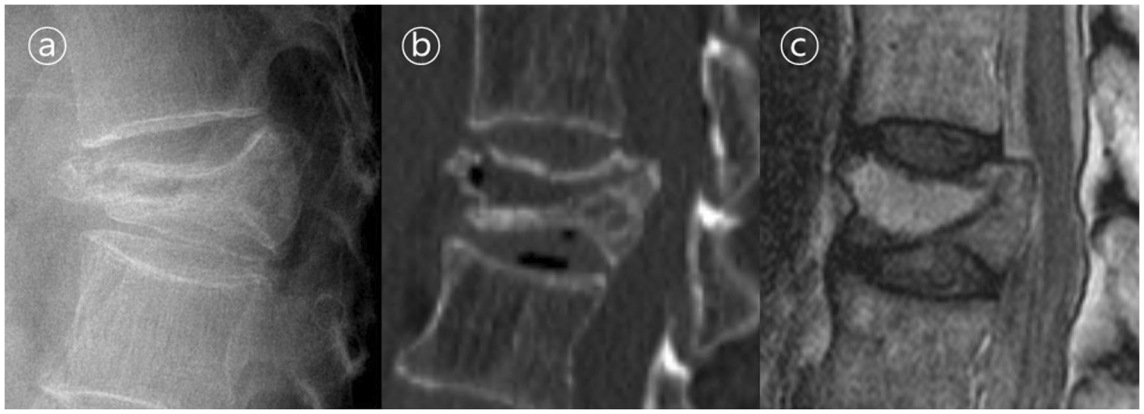

Fig. 1 The intravertebral cleft (IVC) sign. **a**, **b** It appears as a horizontal and linear radiolucent shadow within the vertebral body on the plain radiograph and CT. **c** It appears as high signal intensity (this case) or low signal intensity on T2-weighted images on MRI according to the content of fluid or gas within the cleft, respectively. Compared to collapsed IVC on the plain radiograph taken in the standing position, a wide gap of IVC is noted on CT and MRI taken in the supine position

Results

General demographic data of included patients are shown in Table 1. There was no significant difference in BMD score, BMI, or initial NRS among the three groups. The mean age was significantly higher in group III (75.7 ± 10.1 years) than that in group I (71.6 ± 8.1 years) or group II (70.0 ± 8.2 years) ($p = 0.016$). Mean initial height loss (HL) was significantly higher in group III (37.6 ± 18.1%) than that in group I (24.8 ± 13.9%) or group II (21.7 ± 12.6%) ($p < 0.001$). The mean initial ODI was also higher in group III (71.0 ± 15.5) than that in group I (61.2 ± 8.8) or group II (61.0 ± 7.9) ($p = 0.005$). For MR classification, type I (endplate type) was dominant in three groups (group I, 72%; group II, 75%; and group III, 86%) over type II (mid-portion type) (group I, 28%; group II, 25%; and group III, 14%). For fracture level, thoracolumbar area was the main location in three groups (group I, 72%; group II, 68%; and group III, 62%).

Clinical and radiologic results are demonstrated in Table 2. There was no significant difference in NRS, HL, or kyphotic angle (KA) at the last follow-up among the three groups. The ODI on the last follow-up was significantly higher in group III (36.4 ± 16.6) than that in group I (28.9 ± 8.8) and group II (26.4 ± 6.2) ($p = 0.009$); however, changes of the ODI were similar among the groups (Fig. 4a). Also, the degree of NRS improvement was better in group III (5.7 ± 2.1) than that in group I (3.1 ± 2.2) or group II (3.5 ± 1.7) ($p < 0.001$) (Fig. 4b). Regarding the radiologic parameters, the change of HL was much smaller in group III (5.8 ± 11.2) than that in group I (13.9 ± 15.8) or group II (14.3 ± 15.3) ($p = 0.042$). The total number of cases with the presence of IVC sign was 30. Rate of IVC sign was lower in group III (7.4%) than that in group I (20.5%) and group II (30.3%), although the difference was not statistically significant ($p = 0.053$). Fracture instability defined as dynamic instability at fracture level of the supine and standing radiography occurred in three patients in group I, three patients in group II, and one patient in group III.

Risk factor analyses of impaired fracture healing for IVC presence, increase of KA (≥ 10°), and increase of HL (≥ 15%) are presented in Table 3. In univariate analysis for IVC presence, MRI classification type II and PTH medication had *p*-values less than 0.2. In multivariate analysis, MRI classification type II and PTH medication were significantly associated with IVC presence. The only risk factor related to increase of KA for more than 10° was MRI classification type II in multiple regression analysis. In univariate analysis for increase of HL for more than 15%, sex, MRI classification type II, and PTH medication had *p* values less than 0.2. However, only

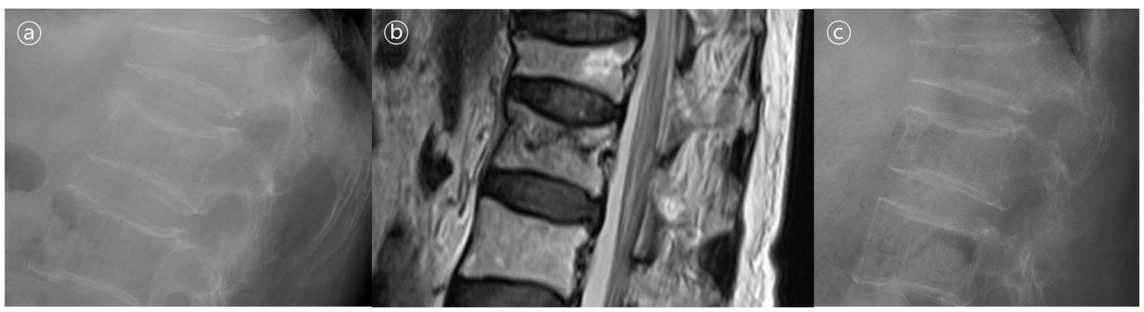

Fig. 2 **a**, **b** A 76-year-old woman was diagnosed with an osteoporotic spinal fracture at L1, type I endplate type. **c** She was treated with teriparatide, and there was no intravertebral cleft and further collapse on 3 months post-injury image

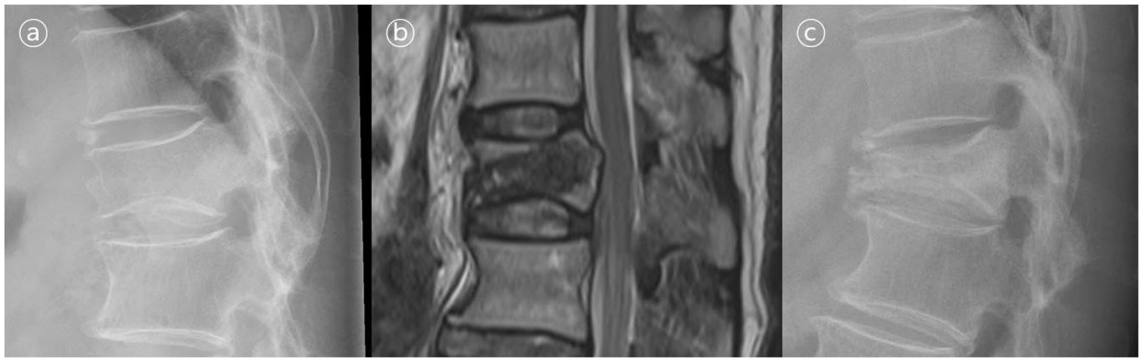

Fig. 3 **a**, **b** A 67-year-old woman was diagnosed with an osteoporotic spinal fracture at D12, type II mid-portion type. **c** She was treated with bisphosphonate, and there was intravertebral cleft and further collapse on 3 months post-injury image

Table 1 Demographic data of the study subjects

	Group I ($n = 39$)	Group II ($n = 66$)	Group III ($n = 27$)	p value	Post hoc test		
					P1	P2	P3
Age (years)	71.6 ± 8.1	70.0 ± 8.2	75.7 ± 10.1	*.016*			
					.-		
168							
	.005	*.003*					
BMD (T-score)	− 3.7 ± 1.1	− 3.7 ± 0.8	− 3.7 ± 0.8	.854			
					.-		
596							
	.910	.682					
BMI (kg/m^2)	23.3 ± 3.2	24.2 ± 3.6	24.2 ± 4.0	.234			
					.-		
091							
	.480	.404					
Initial HL (%)	24.8 ± 13.9	21.7 ± 12.6	37.6 ± 18.1	*.000*			
					.-		
218							
	.000	*.005*					
Initial NRS	6.7 ± 1.8	6.8 ± 1.8	8.7 ± 1.8	.055			
					.-		
405							
	.000	*.000*					
Initial ODI (%)	61.2 ± 8.8	61.0 ± 7.9	71.0 ± 15.5	*.005*			
					.-		
649							
	.003	*.004*					
MRI classification (*N*)				.957			
Type I	28 (72%)	50 (75%)	20 (86%)				
Type II	11 (28%)	16 (25%)	7 (14%)				
Fracture location (*N*)				.230			
Thoracic	3 (7.5%)	6 (9.3%)	5 (19%)				
Thoracolumbar	28 (72%)	45 (68%)	17 (62%)				
Lumbar	8 (20.5%)	15 (22.7%)	5 (19%)				

All values are mean ± SD. P1 = showing difference between group I and group II, P2 = showing difference between group II and group III, P3 = showing difference between group I and group III, statistical significant p value was marked in *italics*

BMD bone mineral density, *BMI* body mass index, *HL* height loss, *NRS* numerical rating scale, *ODI* Oswestry disability index, *MRI* magnetic resonance imaging

Table 2 Clinical and radiological results of the study subjects

	Group I ($n = 39$)	Group II ($n = 66$)	Group III ($n = 27$)	p value	Post hoc test		
					P1	P2	P3
Change from baseline in NRS	3.1 ± 2.2	3.5 ± 1.7	5.7 ± 2.1	*0.000*	0.333	*0.000*	*0.000*
Change from baseline in ODI (%)	32.3 ± 9.0	35.1 ± 8.9	36.0 ± 17.2	0.371	0.212	0.736	0.272
Change from baseline in HL (%)	13.9 ± 15.8	14.3 ± 15.3	5.8 ± 11.2	*0.042*	0.705	*0.019*	*0.032*
Change from baseline in KA (°)	5.5 ± 5.8	6.0 ± 8.8	8.4 ± 7.2	0.254	0.233	0.384	0.152
Presence of IVC (*N*)	8 (20.5%)	20 (30.3%)	2 (7.4%)	0.053	*0.031*	*0.020*	*0.022*
Fracture instability (*N*)	3 (7.7%)	3 (4.5%)	1 (3.7%)	0.692	0.467	0.935	0.504

All values are mean ± SD. P1 = showing difference between group I and group II, P2 = showing difference between group II and group III, P3 = showing difference between group I and group III, statistical significant p value was marked in *italics*

NRS numerical rating scale, *ODI* Oswestry disability index, *HL* height loss, *KA* kyphotic angle, *IVC* intravertebral cleft

MRI classification type II and PTH medication were significantly associated with increase of HL in multivariate analysis.

Discussion

For elderly patients, OSFs still cause high morbidity and mortality, although conservative treatment is effective [2]. For several decades, many kinds of anti-osteoporosis medication have been used for prevention of OSFs and fracture healing during conservative treatment period. Several studies have shown that the prevented aspect of anti-osteoporosis medications is effective for OSFs [6]. However, anti-osteoporosis medications, especially anti-resorptive agents, have negative effects on fracture healing due to excessive suppression of physiologic bone turnover [11–13]. Anabolic agents such as PTH can increase bone formation by improving osteoblast function and lifespan [15]. In animal studies, PTH can improve callus quality and quantity [22, 23]. Seki et al. [24] have reported that daily PTH usage can enhance spinal fusion and reduce adjacent segmental fractures in adult deformity surgery for osteoporosis patients. Although several clinical studies have presented that PTH may enhance bone healing, the effect of PTH on the healing of the fracture remains uncertain. Peichl et al. [17] and Ha et al. [25] have presented that union rates at 8 weeks after trauma are higher in the PTH group than those in the control group (pubis 100% vs. 9.1%, $p < 0.001$; and sacrum 100% vs. 20%, $p < 0.001$) for pubic and sacral osteoporotic fractures. On the other hand, Aspenberg et al. [26] have reported that the union rate and time to union are similar between PTH and control groups for osteoporotic pertrochanteric femur fractures after surgery.

In our study, PTH usage significantly reduced IVC presence (odds ratio 0.160; 95% CI 0.029–0.877, $p = 0.035$). The presence of IVC was also much lower in group III (7.4%) than that in group I (20.5%) or group II (30.3%), although the difference was not statistically significant. Impaired healing of OSFs can lead to many serious problems such as intractable pain, kyphotic deformity, and neurologic compromise [27–29]. However, the pathogenesis and significance of IVC in OSF patients remain unclear. Many authors have suggested that IVC sign due to avascular necrosis is a portent of impaired fracture healing following OSFs [30–32]. Tsuchie et al. [18] have reported that the presence of IVC is significantly lower in daily PTH group than that in the group taking risedronate (5% vs. 42.9%, $p < 0.05$). Fabbriciani et al. [33] have reported that vacuum decreased and back pain improved after PTH treatment. Iwata et al. [34] have shown a significantly ($p = 0.026$) higher radiologic union rate at 6 months in the group taking PTH (89%) than that in the group taking BP (68%), with adjusted odds ratio

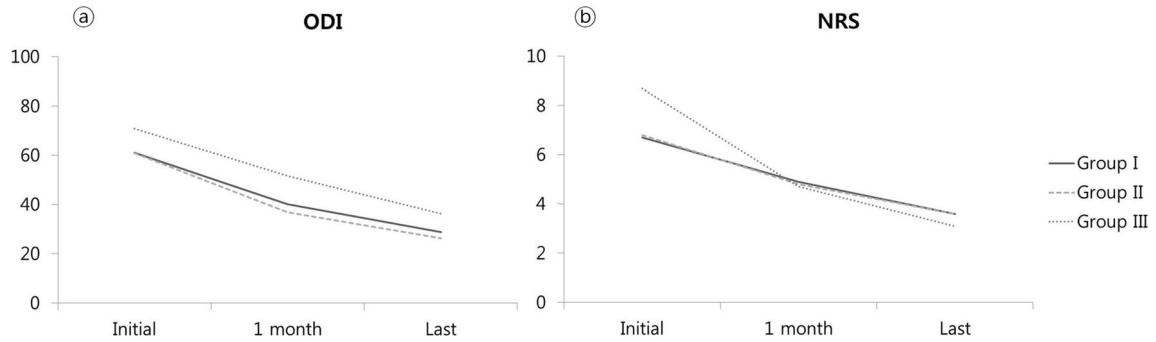

Fig. 4 **a** Oswestry disability index (ODI) of each group at initial, 1 month, and last. **b** Numerical rating scale (NRS) of each group at each time

Table 3 Univariate and multivariate regression analysis: role of parameters on IVC presence, changing in kyphosis (KA ≥ 10°), and changing in height (HL ≥ 15%) after 3 months from this cohort

	Univariate analysis ($n = 132$)			Multivariate analysis ($n = 132$)		
Variables	Beta	OR (95% CI)	p value	Beta	95% CI	p value
IVC						
Age	− 0.015	0.985 (0.935–1.036)	0.554			
Sex	0.442	1.556 (0.564–4.290)	0.393			
BMD	− 0.434	0.648 (0.388–1.083)	0.648			
BMI	− 0.027	0.973 (0.854–1.110)	0.686			
MRI classification	1.698	5.465 (2.114–14.129)	*0.000*	2.040	7.691 (2.597–22.777)	*0.000*
Medication						
No medication	− 0.536	0.585 (0.218–1.569)	0.086	− 0.880	0.415 (0.129–1.336)	0.072
BP	− 1.707	0.181 (0.038–0.866)	0.287	− 1.830	0.160 (0.029–0.877)	0.140
PTH			*0.032*			*0.035*
Changes of KA ≥ 10°						
Age	0.045	1.046 (0.996–1.098)	0.073	0.036	1.036 (0.980–1.0960)	0.213
Sex	0.436	1.547 (0.604–3.963)	0.363			
BMD	− 0.397	0.672 (0.420–1.077)	0.099	− 0.295	0.745 (0.439–1.264)	0.745
BMI	− 0.007	0.993 (0.884–1.115)	0.905			
MRI classification	1.698	5.465 (2.114–14.129)	*0.006*	1.338	3.812 (1.515–9.595)	*0.004*
Medication						
No medication	0.796	2.216 (0.805–6.101)	0.122	0.914	2.494 (0.864–7.201)	0.067
BP	− 0.664	0.515 (0.209–1.270)	0.123	− 0.664	0.433 (0.166–1.128)	0.091
PTH			0.045			0.087
Changes of HL ≥ 15%						
Age	0.009	1.009 (0.964–1.057)	0.687			
Sex	1.431	4.182 (1.652–10.584)	*0.014*	1.239	1.418 (0.507–3.966)	0.506
BMD	− 0.225	0.799 (0.508–1.255)	0.799			
BMI	− 0.010	0.990 (0.882–1.110)	0.860			
MRI classification	1.697	5.457 (2.241–13.289)	*0.000*	1.563	4.773 (1.900–11.988)	*0.001*
Medication						
No medication	0.796	1.425 (0.585–3.471)	*0.110*	0.914	1.747 (0.636–4.797)	*0.116*
BP	− 1.487	0.226 (0.050–1.030)	*0.436*	− 0.797	0.325 (0.094–1.130)	*0.279*
PTH			*0.044*			*0.029*

IVC intravertebral cleft, *KA* kyphotic angle, *HL* height loss, *OR* odds ratio, *CI* confidence interval, *BMD* bone mineral density, *BMI* body mass index, *MRI* magnetic resonance imaging, *BP* bisphosphonate, *PTH* parathyroid hormone, statistical significant p value was marked in *italics*

of 8.15 (95% CI 2.02–43.33). Presence of IVC is not a perfect representation of the occurrence of non-union or its following complications. However, due to the lack of research, our results are expected to be meaningful. Thus, PTH might play an important role in the healing process of OSFs.

The current study showed that change of vertebral height was significantly lower in group III (5.8 ± 11.2) than that in group I (13.9 ± 15.8) and group II (14.3 ± 15.3) ($p = 0.042$). PTH usage also significantly reduced the risk of changing vertebral height (HL ≥ 15%) (odds ratio 0.325; 95% CI 0.094–1.130, $p = 0.029$). However, change of local KA at index vertebra had no significant difference among the three groups. PTH usage was not related to change in kyphosis (KA ≥ 10°) either. Tsuchie et al. [18] have reported similar outcomes. Change of vertebral collapse was significantly lower in daily PTH group than that in the control group ($p < 0.01$) and the group taking risedronate ($p < 0.05$) at 8 weeks and 12 weeks ($p < 0.01$) after treatment. Furthermore, change of KA was significantly lower in the daily PTH group than that in the control group ($p < 0.01$) and the risedronate group ($p < 0.05$) at 8 weeks after treatment. According to these results, it can be concluded that PTH is effective for reduction of collapse progression. However, Iwata et al. [34] have reported that change of body height ($p = 0.228$) or local KA ($p = 0.495$) had no significant difference between PTH group and alendronate group. In our study, group II had two different categories: alendronate ($n = 50$) and risedronate ($n = 16$). However, the above two studies [18, 34] included alendronate and risedronate, respectively. These conflicting results could be due to the variety of BPs used in these studies.

In the present study, improvement of NRS was significantly higher in group III (5.7 ± 2.1) than either group I (3.1 ± 2.2) or group II (3.5 ± 1.7) ($p < 0.001$), although the improvement of ODI score had no significant difference among the three groups. Tsuchie et al. [18] have also reported that visual analogue scale (VAS) in daily PTH group was lower than that in the risedronate group at 8 and 12 weeks after treatment ($p < 0.05$). NRS at the last follow-up showed no significant difference among the three groups in our results. Similar result was also found in terms of positive effect on back pain improvement. Hadji et al. [35] have reported that there is no significant difference between PTH group and risedronate group. The proportion of patients with worst back pain was reduced over 30% at 6 months ($p = 0.64$), 12 months ($p = 0.68$), and 18 months ($p = 0.60$). The proportion of patients with average back pain was also reduced over 30% at 6 months ($p = 0.81$), 12 months ($p = 0.99$), and 18 months ($p = 0.40$). There may be some hypotheses about the mechanism for the reduction of back pain in patients with vertebral fractures. First, teriparatide may enhance fracture healing owing to its anabolic action. Iwata et al. [34] and Kitaguchi et al. [36] reported that OSF patients who received teriparatide treatment showed early union compared to control group. Meanwhile, there is some controversy about the effect of anti-resorptive agents on fracture union. Their suppressive action on osteoclastic activity can inhibit bone remodeling, which is crucial for fracture healing. Second, teriparatide itself may have a pain-reducing effect. An animal study about pain relief mechanism of PTH has demonstrated that the inhibitory effect on inflammatory cytokine expression such as IL-1β, IL-6, and TNF-α might be related to the pain reduction effect of PTH [37]. However, detailed knowledge about this mechanism remains unclear. More research is needed to clarify the mechanism involved in the effect of PTH.

This study has a few limitations. First, this is a retrospective study with prospective design, relatively few cohorts, and heterogeneity that could have selection bias. In demographic data, age and initial HL were significantly higher in group III than those in the other two groups. PTH is usually used for patients with higher risk because of its positive effects on fracture healing and pain relief. Although initial and last ODI scores were higher in group III than those in the other two groups, improvement of ODI score was not significantly different among the three groups. This result can be seen in the same sense. Although we used multiple regression analysis to adjust heterogeneity, a well-designed prospective study with a large cohort is essential to improving our knowledge for OSFs. Second, there was a lack of explanation about biomarkers such as bone turn-over markers, vitamin D level, and serum calcium level. Further investigation including these markers will help us understand biomechanisms of PTH better. Third, as mentioned above, diversity BPs such as alendronate and risedronate were used. Further studies would require a comparison of each medication to produce more accurate results.

OSFs can lead to neurologic compromise despite conservative treatments in some cases [38]. Several studies have reported that neurologic compromise is related to nonunion or malunion [30–32]. For this reason, early treatment for OSFs is thought to be important. Several factors could be involved. The use of medication could also influence the outcome. More studies are needed. In conclusion, different types of anti-osteoporosis medication during the initial phase following acute OSFs presented different clinical and radiological results. Although this study has several limitations, results of this study suggest that the use of anabolic agent can significantly enhance fracture healing, reduce progressive collapse, and present good pain relief. These findings suggest that proper selection of medication could improve initial management of acute OSFs.

Funding This study was partially supported by investigator initiated trial funded by Dong-A Pharmaceuticals.

Compliance with ethical standards

Conflicts of interest None.

Ethical issues This study was performed through retrospective analysis of clinical and radiological data. Approval of institutional review board was obtained before this submission.

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