Retrospective Analysis

Effect of Epidural Steroid Injection on Bone Mineral Density in Postmenopausal Women According to Antiosteoporotic Medication Use

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Background: No studies to date have compared bone mineral density (BMD) changes after epidural steroid injection (ESI) between postmenopausal patients taking antiosteoporotic medication and those who are not.

Objective: The aim of the present study was to analyze the relationship between ESI and BMD changes in postmenopausal patients according to antiosteoporotic medication use.

Study Design: Retrospective analysis.

Setting: Department of Anesthesiology and Pain Medicine at Asan Medical Center, Korea.

Methods: We retrospectively analyzed postmenopausal women who underwent ESI using dexamethasone. All women had received a diagnosis of lumbar spinal stenosis and their BMD had been measured before and after treatment. BMD was evaluated by dual-energy x-ray absorptiometry at the lumbar spine, femoral neck, femoral trochanter, and total femur, and was recorded as absolute g/cm2 and T-scores. A total of 126 patients were included in the final analysis. ESI patients were grouped as follows: group 1 (n = 74) ESI patients who took antiosteoporotic medication; group 2 (n = 52) ESI patients who did not take antiosteoporotic medication.

Results: In group 1, there were no significant differences between baseline and post-treatment BMD absolute values (g/cm2) in the lumbar spine, femoral neck, femoral trochanter, and total femur. In group 2, significant changes in the post-treatment BMD absolute values (g/cm2) from baseline were observed in the femoral neck (–1.48 ± 3.84%), femoral trochanter (–2.80 ± 7.50%), and total femur (–2.23 ± 4.52%), but not in the lumbar spine (–2.23 ± 4.52%).

Limitations: This study contained a small sample size, no control group, and no long-term follow-up of the BMD changes after ESI.

Conclusions: Our data provide new evidence indicating that ESI causes BMD changes in postmenopausal women who do not take antiosteoporotic medication. Thus, we recommend that prophylactic antiosteoporotic treatment be considered for postmenopausal women who require ESI treatment.

Keywords: Glucocorticoid, osteoporosis, bone mineral density, epidural steroid injection, antiosteoporotic medication, postmenopausal women, dexamethasone

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Lumbar epidural steroid injections (ESIs) are widely used to treat chronic axial lower back pain and radicular pain from spinal stenosis, herniated discs, and acute pain conditions (1-4). However, glucocorticoids have multiple side effects, including glucocorticoid-induced osteoporosis (GIOP). GIOP is the most common form of both secondary osteoporosis and iatrogenic osteoporosis (5,6). Patients who

receive exogenous glucocorticoids have a dramatically increased risk of fragility fractures after the initiation of glucocorticoid therapy (7,8). The increase in the incidence of fragility fractures is particularly rapid in postmenopausal women (9).

To prevent GIOP, the National Osteoporosis Guideline Group recommended in 2013 that health care providers insist on antiosteoporotic medication for postmenopausal women, such as bisphosphonates, hormone therapy, and adequate calcium and vitamin D (10). Although treatment protocols are well established (11-15), some postmenopausal patients do not regularly receive preventive medicine. One survey found that some patients do not accept the treatment due to a lack of confidence in the effectiveness of antiosteoporotic medication, fear of side effects, lack of trust in the physician, the cost of therapy, and the complexity of the dosing regimen (16).

Previous studies have reported that ESI therapy using triamcinolone or methylprednisolone had no significant effect on bone mineral density (BMD) (17,18). However, the patients were not divided into groups according to antiosteoporotic medication use in those studies. Although dexamethasone is not only one of the most frequently used glucocorticoids for ESI, but is also 25 times more potent than cortisol in its glucocorticoid effect (19), no study to date has examined BMD changes after ESI using dexamethasone. Accordingly, the aim of our current retrospective study was to analyze the relationship between ESI and BMD changes in postmenopausal patients with lower back pain due to radiculopathy according to the administration of antiosteoporotic medication.

Methods

We retrospectively analyzed the patient database of our institute with approval from our Institutional Review Board (number: S2014-2159-0002). Between March 2010 and December 2015, 1,498 postmenopausal patients underwent ESI for treatment of low back pain at our pain clinic and had undergone both a pretreatment and post-treatment (range: 9 months to 2 years) dual-energy x-ray absorptiometry (DEXA) scan. BMD was measured using a Lunar DEXA scanner (Prodigy; Madison, WI) at the lumbar spine, femoral neck, femoral trochanter, and total femur, and was recorded as absolute g/cm2 and T-scores. BMD comparisons were only performed if the patient had a post-treatment DEXA on the same machine as the initial pretreatment DEXA.

Postmenopausal women who underwent ESI using dexamethasone with a diagnosis of lumbar spinal stenosis, and had BMD assessments performed before and after treatment, were included. Patients were excluded if they had used drugs known to affect bone metabolism or had a history of any osteoporotic fracture, hyperparathyroidism, or previous lumbar spine surgery. Patients who had chronic inflammatory conditions, such as asthma, inflammatory bowel disease, or rheumatoid arthritis, or who often used glucocorticoids over long periods of time, were also excluded. Only 126 patients met the inclusion criteria and were therefore included in the final analysis. Patients were grouped as follows: group 1 comprised 74 patients who received ESI using dexamethasone while on antiosteoporotic medication [bisphosphonates (risedronate sodium, ibandronate sodium, alendronate sodium), calcium and vitamin D supplementation, selective estrogen receptor modulators (raloxifene, tamoxifen), hormone therapy]; group 2 comprised 52 patients who underwent ESI using dexamethasone while not on any antiosteoporotic medication.

Body mass index (BMI) was calculated as weight (kilograms) divided by the square of the body height (meters squared). BMD was assessed using DEXA. The rate of change in the BMD was expressed as the annualized percentage of the difference between the post-treatment BMD and the pretreatment BMD divided by the initial BMD. BMD values are expressed as T-scores and changes from the pretreatment values. BMD measurements were repeated within 2 years of treatment. The mean interval from the baseline BMD to the post-treatment BMD was 19.14 months in group 1 and 19.75 months in group 2.

Statistical Analysis

Data were expressed as mean ± standard deviation. Differences in age, BMI, baseline BMD, duration of BMD measurement, total number of ESI(s) performed, mean range between the ESI(s) and the post DEXA study, and mean dose of dexamethasone were compared between the groups using an unpaired t-test. A paired t-test was used to analyze changes in BMD compared with baseline within each group. All statistical tests were two-sided, and a *P* value less than 0.05 was considered statistically significant. SPSS for Windows (version 21; IBM SPSS Inc., Chicago, IL) was used for all statistical analysis.

Results

A total of 126 patients were enrolled in the present study, 74 in group 1 and 52 in group 2. Table 1 lists

the baseline characteristics of each group. No statistically significant differences were observed between the groups with respect to age, weight, height, BMI, duration of BMD monitoring, baseline BMD, total number of ESI(s) performed, mean range between the ESI(s) and the DEXA study, and mean total dose of dexamethasone. The mean changes between the baseline and post-treatment BMD in ESI patients who received antiosteoporotic medication (group 1) were 1.25 ± 6.01% in the lumbar spine, 0.45 ± 4.05% in the femoral neck, 0.39 ± 7.87% in the femoral trochanter, and 0.21 ± 3.64% in the total femur region (Fig. 1). There were no significant differences between baseline and post-treatment values. BMD absolute values (g/cm2) in

Table 1. *Patient characteristics and the mean total dose of dexamethasone.*

	Group 1	Group 2	*P* value
Age (years)	69.51 ± 5.98	67.38 ± 6.25	0.056
Weight (kg)	55.75 ± 8.12	57.27 ± 7.57	0.290
Height (cm)	152.35 ± 6.32	153.18 ± 5.24	0.439
BMI (kg/m2)	24.65 ± 3.18	24.73 ± 3.62	0.476
Duration of BMD monitoring (months)	19.14 ± 6.03	19.75 ± 6.12	0.577
Baseline BMD (g/cm2)			
Lumbar spine	0.88 ± 0.17	0.92 ± 0.14	0.162
Femoral neck	0.71 ± 0.09	0.74 ± 0.10	0.091
Femoral trochanter	0.62 ± 0.12	0.65 ± 0.10	0.112
Total femur	0.78 ± 0.13	0.80 ± 0.11	0.312
Number of ESIs performed	3.62 ± 1.71	3.63 ± 1.91	0.968
Mean range between the ESI(s) and the post DEXA study (months)	16.18 ± 6.03	15.23 ± 5.61	0.375
Mean total dose of dexamethasone (mg)	9.73 ± 6.35	8.94 ± 4.78	0.451

BMI = body mass index; BMD = bone mineral density; ESI = epidural steroid injection; DEXA = dual-energy X-ray absorptiometry.
Group 1: Patients receiving ESI who took antiosteoporotic medication.
Group 2: Patients receiving ESI who did not take antiosteoporotic medication.

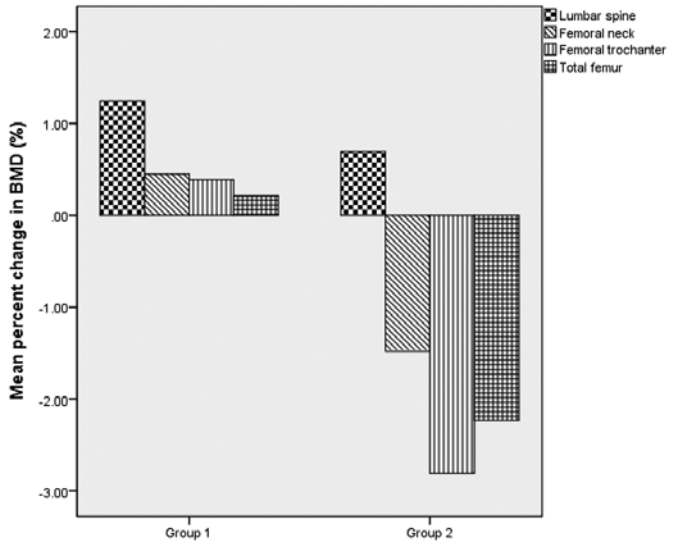

Fig. 1. *Mean percentage changes in bone mineral density (BMD) from baseline.*
Group 1: Patients receiving ESI who took antiosteoporotic medication.
Group 2: Patients receiving ESI who did not take antiosteoporotic medication.

the lumbar spine (paired t-test: t = –1.302, df = 73, *P* = 0.197), femoral neck (paired t-test: t = –0.574, df = 73, *P* = 0.568), femoral trochanter (paired t-test: t = 0.124, df = 73, *P* = 0.902), or total femur (paired t-test: t = -0.067, df = 73, *P* = 0.947). Table 2 lists the mean changes in BMD from baseline for the 5 different antiosteoporotic medications. In subgroup analysis, the BMD of the lumbar spine (1.10 ± 6.76%) and femoral neck (0.87 ± 5.30%) increased in patients treated with risedronate sodium. The BMD of the lumbar spine (1.88 ± 4.42%), femoral trochanter (2.74 ± 6.46%), and total femur (0.69 ± 3.31%) was found to increase in patients treated with ibandronate sodium. The BMD of the lumbar spine (2.84 ± 5.26%), femoral neck (0.46 ± 2.86%), femoral trochanter (1.10 ± 6.75%), and total femur (1.06 ± 3.52%) increased in cases treated with alendronate sodium. The BMD of the femoral neck (4.40 ± 3.10%) and total femur (1.01 ± 2.71%) increased in patients treated with raloxifene hydrochloride. In patients treated with calcium and vitamin D, the mean BMD decreased after ESI (Fig. 2).

The mean changes in BMD in ESI patients who did not receive antiosteoporotic medication (group 2) were 0.69 ± 6.94% in the lumbar spine, –1.48 ± 3.84% in the femoral neck, –2.80 ± 7.50% in the femoral trochanter, and –2.23 ± 4.52% in the total femur region (Fig. 1). Significant changes in the BMD absolute values (g/cm2) from baseline BMD were observed in the femoral neck (paired t-test: t = 3.15, df = 51, *P* = 0.003), femoral trochanter (paired t-test: t = 2.761, df = 51, *P* = 0.008), and

Table 2. *Mean percentage changes in bone mineral density from baseline for the 5 different antiosteoporotic medications.*

Medication		Lumbar spine	Femoral neck	Femoral trochanter	Total femur
Risedronate sodium (n = 23)	Mean	1.10%	0.87%	-2.28%	-0.61%
	SD	6.76	5.30	6.36	3.56
Ibandronate sodium (n = 19)	Mean	1.88%	-0.16%	2.74%	0.69%
	SD	4.42	3.30	6.46	3.31
Alendronate sodium (n = 23)	Mean	2.84%	0.46%	1.10%	1.06%
	SD	5.26	2.86	6.75	3.52
Raloxifene hydrochloride (n = 4)	Mean	-2.13%	4.40%	-1.09%	1.01%
	SD	6.63	3.10	5.38	2.71
Calcium and vitamin D (n = 5)	Mean	-2.58%	-3.36%	-4.51%	-6.78%
	SD	1.99	4.48	25.95	11.20

Values are expressed as a mean and standard deviation (SD).
BMD = bone mineral density.

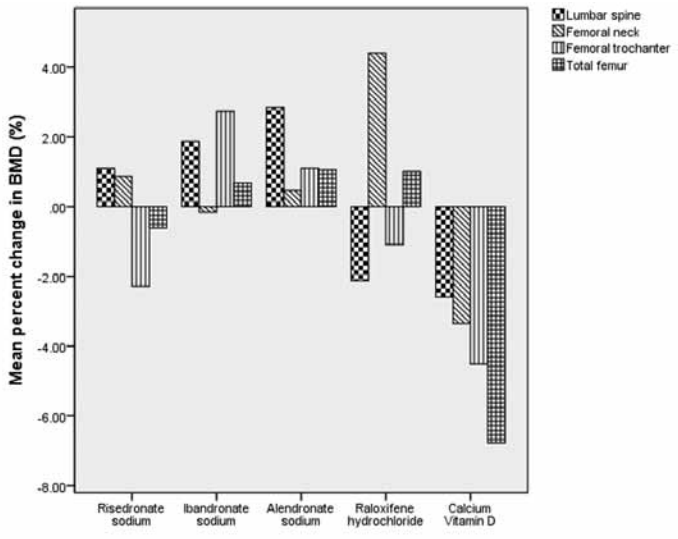

Fig. 2. *Mean percentage changes in bone mineral density (BMD) from baseline.*

total femur (paired t-test: t = 3.753, df = 51, $P < 0.001$), but not in the lumbar spine (paired t-test: t = -0.552, df = 51, $P = 0.584$). The BMD outcomes (normal, osteopenia, or osteoporosis) for the lumbar spine, femoral neck, femoral trochanter, and total femur regions before and after ESI for both groups 1 and 2 are listed in Table 3.

Discussion

No studies to date have compared the BMD changes after ESI between postmenopausal patients who are taking antiosteoporotic medication or not. ESI is the most widely used pain management procedure for treating patients with lower back pain or spinal stenosis who do not respond to other treatments (20,21). However, glucocorticoids affect bone resorption, osteoblast function, osteocyte apoptosis, and calcium balance, and negatively affect sex hormone status in postmenopausal women (22). Qualitative changes in BMD can occur through low-dose glucocorticoid therapy (5,23). GIOP guidelines propose the preventive use of antiosteoporotic medication early in the course of glucocorticoid therapy, particularly in postmenopausal women. At a similar BMD level, postmenopausal women who are treated with glucocorticoids have a higher fracture risk than postmenopausal nonusers of glucocorticoids (5,24).

There have been some comparative studies of ESI and BMD. Manchikanti et al (25) have reported that BMD showed no significant change at any interval within one year after neuraxial steroid injection. They used betamethasone acetate and methylprednisolone acetate and concluded that low-dose administration of neuraxial steroids is safe in patients suffering from chronic pain. In the lumbar spine, our current findings are consistent with previous reports, indicating that the mean change in BMD shows no significant change regardless of antiosteoporotic medication use. However, an association between steroid use and BMD change in the femoral neck, femoral trochanter, and total femur has not been reported previously. Our present results show that the lumbar spine is far less affected than the femur. Our interpretation of these associations is that responders to ESI increase their activity and thereby blunt the negative effects of dexamethasone. Kang et al (17) have reported that ESI treatments using triamcinolone had no significant effect on BMD. Another

Table 3. *Bone mineral density outcomes before and after epidural steroid injection.*

	Baseline Group1	After ESI Group 1	Baseline Group 2	After ESI Group 2
Lumbar spine				
Normal	10/74	9/74	13/52	15/52
Osteopenia	37/74	40/74	30/52	29/52
Osteoporosis	27/74	25/74	9/52	8/52
Femoral neck				
Normal	7/74	9/74	16/52	14/52
Osteopenia	41/74	42/74	21/52	21/52
Osteoporosis	26/74	23/74	15/52	17/52
Femoral trochanter				
Normal	26/74	26/74	21/52	16/52
Osteopenia	39/74	36/74	23/52	26/52
Osteoporosis	9/74	12/74	8/52	10/52
Total femur				
Normal	14/74	16/74	17/52	15/52
Osteopenia	39/74	39/74	26/52	27/52
Osteoporosis	21/74	19/74	9/52	10/52

BMD data are based on T-scores.
Values represent the number of patients/total patients
Osteopenia was defined as a −2.5 SD < BMD T score < −1.0 SD
Osteoporosis was defined as a BMD T-score ≤ −2.5 SD
BMD = bone mineral density; ESI = epidural steroid injection.
Group 1: Patients receiving ESI who took antiosteoporotic medication.
Group 2: Patients receiving ESI who did not take antiosteoporotic medication.

study indicated that a cumulative dose of less than 3 g methylprednisolone had no effect on BMD (18). Our current findings in patients receiving antiosteoporotic medication (group 1) are consistent with those of previous reports. The mean BMD changes in ESI patients who received antiosteoporotic medication were 1.25 ± 6.01% in the lumbar spine, 0.45 ± 4.05% in the femoral neck, 0.39 ± 7.87% in the femoral trochanter, and 0.21 ± 3.64% in the total femur region.

In contrast, Al-Shoha et al (26) indicated in their study that a single ESI in postmenopausal women induced an average BMD decrease of 1.8%, and that the metabolic glucocorticoid effect increased the rate of bone turnover. Thus, these authors recommend prophylactic treatment for postmenopausal women who are to receive ESI. Our current study also showed that ESI treatment using dexamethasone increased the fragility fracture risk in patients not taking antiosteoporotic medication (group 2). The mean changes in BMD in our ESI patients who were not on antiosteoporotic medication were –1.48 ± 3.84% in the femoral neck, –2.80 ± 7.50% in the femoral trochanter, and –2.23 ± 4.52% in the total femur region. Furthermore, the fracture risk increases with the glucocorticoid dose, before changes are seen on imaging studies such as DEXA (27).

Some pharmacological agents are available for the management and prevention of GIOP, by either decreasing bone resorption or stimulating formation of new bone tissue (28). Several studies have shown that the most effective antiosteoporotic therapy for the treatment and prevention of GIOP is bisphosphonates, which reduce fracture risk and prevent bone loss (22,27,29,30). Woolf (22) has suggested that the most effective bisphosphonates are risedronate and alendronate. Moreover, he recommended that these drugs be used at the beginning of glucocorticoid therapy. Ibandronate has also been found to decrease the rate of vertebral fractures in some studies (5,31). From our present results, the BMD of the lumbar spine and femoral neck increased in patients treated with risedronate sodium. The BMD of the lumbar spine, femoral neck, femoral trochanter, and total femur also increased in cases treated with alendronate sodium. Finally, the BMD of the lumbar spine, femoral trochanter, and total femur was found to increase in patients treated with ibandronate sodium.

Raloxifene hydrochloride has been evaluated in previous studies (5,32) and found to improve BMD in postmenopausal women receiving prednisone. In our current study, the BMD of the femoral neck and total femur increased in patients treated with raloxifene hydrochloride. According to a previous report calcium and vitamin D are insufficient to prevent osteoporotic fractures in patients treated with glucocorticoids. These authors reported that calcium and vitamin D supplementation are far less effective than other antiosteoporotic medications in preventing osteoporosis (5,32). Our present data are in agreement with these previous review articles. In our current study patients treated with calcium and vitamin D, the mean BMD decreased after ESI.

The steroidal agents now in common use include dexamethasone, methylprednisolone acetate, and triamcinolone. Of these steroids, we prefer to use dexamethasone when performing transforaminal ESI, because methylprednisolone and triamcinolone have densely packed particles. Also, when diluted in local anesthetic, both methylprednisolone and triamcinolone may form large aggregations that can block smaller arteries and arterioles. There have been several reported cases of central nervous system sequelae after transforaminal ESI, including occlusion of the segmental artery accompanying the nerve root by the particulate steroid or embolization of the particulate steroid through the vertebral artery (33). Additionally, Chiller et al (34) have reported that fungal meningitis is associated with contaminated methylprednisolone injections. These fungal infections showed substantial morbidity and mortality. Thus, a nonparticulate steroid such as dexamethasone is preferred for transforaminal ESI. However, dexamethasone sodium phosphate has significantly stronger glucocorticoid effects than either methylprednisolone or triamcinolone. Dexamethasone has little or no mineralocorticoid activity. The increased glucocorticoid potency of dexamethasone can theoretically result in a higher risk of fragility fractures compared with other steroids (relative glucocorticoid potency: methylprednisolone = 5, triamcinolone = 5, bethamethasone = 33, dexamethasone = 27) (33). In a previous animal study, dexamethasone contributed to bone loss due to a lack of vitamin D bioactivation (35). The pathophysiological mechanism involves inhibition of gastrointestinal calcium absorption by opposing vitamin D activity (36). Therefore, we suggest that physicians ensure that postmenopausal women who undergo ESI using dexamethasone receive osteoporosis prevention therapy.

A previous large population-based longitudinal study demonstrated that the estimated rate of bone

loss at the lumbar spine for postmenopausal women was quadratic at a rate of 3.12% and linear at a rate of 1.67%, for the femoral neck over a 15-year follow-up (37). In our current study, we did not regard the natural history of osteoporosis over only a 2-year interval to be relevant to our analysis. Thus, we did not evaluate the relationships between the effect of the steroid injection and the natural history of osteoporosis.

Our present study had some limitations of note. To reduce any possible selection bias, our inclusion criteria were restrictive. Thus, our sample size was relatively small. However, our 126 study patients were screened from 1,498 patients who had both a pre-treatment and a post-treatment DEXA scan. Second, we did not assess postmenopausal women who did not receive ESI because we focused on BMD changes after ESI. Third, it is uncertain whether the osteoporosis prevention effects are long term and it would be useful to analyze follow-up data after a longer period of time. Fourth, a larger number of patients would be useful to further evaluate the relationship between different steroids (methylprednisolone, betamethasone, or triamcinolone) and BMD changes in postmenopausal patients according to antiosteoporotic medication use. Fifth, our analysis was limited by its retrospective design.

Notwithstanding the aforementioned limitations, this is to our knowledge the first study to compare the BMD changes after ESI between postmenopausal patients taking antiosteoporotic medication or not. Our results suggest that postmenopausal women who undergo ESI require prophylactic treatment with antiosteoporotic medication. Osteoporosis prophylaxis should be promoted by hospitals and pain specialists.

Conclusion

The harmful effects of glucocorticoids on BMD are already known, and an increased risk of fragility fracture is common in postmenopausal women. Our data provide new evidence that ESI causes BMD changes in postmenopausal women who do not take antiosteoporotic medication. Thus, we recommend that prophylactic antiosteoporotic treatment prior to ESI be considered for postmenopausal women.

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