Retrospective Analysis



Influence of Lumbar Epidural Steroid Injection on Osteoporosis and Denosumab Treatment

Jun-Han Kim, MD, Jeong-mo Koo, MD, Dong-Eun Shin, MD, and Tae-Keun Ahn, MD

From: Department of Orthopedic and Spine Surgery, CHA Bundang Medical Center, CHA University, Republic of Korea

Address Correspondence: Tae-Keun Ahn, MD Department of Orthopedic and Spine Surgery, CHA Bundang Medical Center, CHA University 59 Yatap-ro, Bundang-gu, Seongnam-si, Gyeonggi-do 463-712, Republic of Korea E-mail: ajh329@gmail.com

Disclaimer: There was no external funding in the preparation of this article.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

> Article received: 03-17-2024 Revised article received: 09-27-2024 Accepted for publication: 12-09-2024

Free full article: www.painphysicianjournal.com Background: Lumbar epidural steroid injections (ESIs) are commonly used to alleviate pain associated with lumbar disorders. However, administering steroids to patients with osteoporosis may lead to a decline in bone mineral density (BMD) and increase fracture risk. While various steroids are utilized in ESIs, limited research exists on their effect on BMD.

Objectives: This study aimed to analyze the effect of dexamethasone-based ESI therapy on osteoporosis in patients receiving or not receiving denosumab, utilizing real-world clinical data.

Study Design: Retrospective analysis.

Setting: A university hospital orthopedic department.

Methods: A retrospective review was conducted, incorporating patients who underwent denosumab therapy alongside ESIs for pain alleviation from January 2018 through April 2022. Eligibility criteria included patients with a minimum follow-up period of 12 months. Forty patients who had received an ESI and denosumab treatment were enrolled in Group One. Similarly, 35 patients who had only received an ESI (Group 2) and 33 patients who underwent denosumab treatment alone (Group 3) were enrolled and analyzed. Statistical analysis was performed using analysis of variance (ANOVA) to compare patient age, gender, lumbar and hip BMD, difference in lumbar and hip BMD at postinjection one year, serum vitamin D, calcium, phosphorus levels, and one-year cumulative steroid dosage.

Results: In terms of patient demographics, the mean age of Group One was 71.73 (\pm 9.59) years, Group 2 was 70.00 (± 9.82) years, and Group 3 was 71.18 (± 5.64) years. The ANOVA analysis revealed no significant differences among groups. The BMD analysis showed that the lumbar BMD in Group One was 0.811 g/cm², Group 2 was 0.831 g/cm², and Group 3 was 0.822 g/cm². Hip BMD in Group One was 0.696 g/cm², Group 2 was 0.711 g/cm², and Group 3 was 0.668 g/cm². The change in BMD values showed that in Group One, lumbar BMD increased by 0.0411 g/cm² compared to baseline, a 5.06% increase, while hip BMD increased by 0.0047 g/cm², a 0.68% increase. In Group 2, lumbar BMD decreased by -0.0307 g/cm², a 3.7% decrease, and hip BMD decreased by -0.036 g/cm², a 5.02% decrease. In Group 3, lumbar BMD increased by 0.056 g/cm², a 6.77% increase, while hip BMD increased by 0.005 g/cm², a 0.69% increase.

Limitations: The number of patients recruited was relatively small and limited to specific age groups. Study design was retrospective.

Conclusion: Lumbar ESIs with dexamethasone reduce BMD in elderly patients with osteoporosis. However, when denosumab is administered alongside dexamethasone-based ESIs, the steroid does not significantly affect the decline of BMD.

Key words: Steroid, epidural injection, osteoporosis, antiresorptive agent, denosumab, bone mineral density, lumbar spine

Pain Physician 2025: 28:E183-E189

umbar epidural steroid injections (ESIs) are frequently used to treat pain or lumbar disorders such as lumbar disc herniation, degenerative disc disease, and lumbar spinal stenosis. These injections usually deliver steroids with local anesthetics directly to the epidural space around the nerves, reducing inflammation and providing pain relief (1).

Utilizing steroids in patients diagnosed with osteoporosis has been reported to induce a decline in bone mineral density (BMD) (2). Furthermore, this reduction in BMD inherently is known to amplify the vulnerability to fractures, with notable reports suggesting an increased risk of fractures in the vertebral and pelvic bones specifically due to steroid use (2,3).

In lumbar ESIs, steroids are the most essential substance used to reduce inflammation. Various types of steroids are employed, each with different properties and potencies. The most commonly used steroids in ESIs include dexamethasone, betamethasone, methylprednisolone, and triamcinolone. In addition to the lack of research on the effect of epidural steroids on BMD, a number of studies have shown inconsistent findings depending on the kind of epidural steroid, the osteoporotic medications used, and the enrolled patients. Manchikanti, et al (4) reported that following a year of ESIs using methylprednisolone and betamethasone acetate, the BMD stayed unchanged at low dose administration in patients with chronic pain. Another study supported similar conclusions, stating that a lifetime cumulative methylprednisolone dose of at least 3,000 mg is safe for use in healthy men and women (5). Regarding triamcinolone, studies have shown that in women who are postmenopausal who have low back pain, cumulative doses of triamcinolone in ESIs surpassing 200 mg over a 12-month period or 400 mg over a 3-year period may lower BMD (6,7).

Among commonly used steroids, dexamethasone is often preferred due to its nonparticulate and water-soluble nature, which reduces the risk of complications associated with particulate steroids like triamcinolone (8).

Denosumab is a monoclonal antibody medication used to treat osteoporosis, including glucocorticoid-induced osteoporosis. Denosumab acts by blocking RANK ligand (RANKL), a protein necessary for osteoclasts to develop, function, and survive. Denosumab decreases bone resorption and raises bone density by inhibiting RANKL (9).

To date, few studies have reported the effect of dexamethasone in ESIs on BMD in patients with osteo-

porosis. Furthermore, no study has been released on the effect of denosumab on BMD in patients with osteoporosis receiving dexamethasone-based ESI therapy. Therefore, we aimed to compare and analyze the effect of dexamethasone-based ESI therapy on osteoporosis in patients who had received denosumab and those who had not, by using real-world clinical data.

METHODS

Study Population

This study was conducted with the approval of the CHA Bundang Medical Center, CHA University, Institutional Review Board (IRB No. 2022-09-037-004). It is a retrospective analysis of medical records of patients who underwent a transforaminal ESI by one orthopedic surgeon in the same manner and/or received denosumab treatment. The patients were selected from those who were treated at a single institutional orthopedic department from January 2018 through April 2022, and who met the criteria of this study.

Exclusion criteria were patients with osteoporotic fractures in the spine or pelvis, those with spine infections, metabolic syndromes, thyroid syndromes, tumors, or those who did not undergo a BMD follow-up or outpatient visits for more than a year.

Among the patients who had received an ESI, a total of 40 were selected for Group One, which comprised patients who also had received denosumab treatment. Group 2 consisted of 35 patients who had received an ESI only; their demographics were matched to those of Group One. Group 3 comprised 33 patients who were undergoing denosumab treatment; their demographics were similarly matched. Additionally, calcium and vitamin D supplements were administered to all patient groups.

BMD tests were conducted in all patient groups, and a follow-up was performed after one year. The BMD measurements were carried out using dualenergy x-ray absorptiometry, which is recognized as the most appropriate BMD measurement method for applying the World Health Organization's diagnostic criteria, as outlined in the guidelines of the International Society for Clinical Densitometry (10,11). Measurements were taken for both the femur and lumbar spine (L1-L4), and the data were collected in units of g/cm². Our study evaluated the utility of manual analysis methods in BMD test results using dual-energy x-ray absorptiometry.

The steroid used was dexamethasone 5 mg/mL

per single injection, calculated by equivalent dosage conversions. We converted 1.5 mg of dexamethasone to be equivalent to 8 mg of triamcinolone, 8 mg of methylprednisolone, 10 mg of prednisone, 10 mg of prednisone, 40 mg of hydrocortisone, and 50 mg of cortisone, based on a previous study (12). Therefore, in our study, since 1.5 mg of dexamethasone was assumed to be an equivalent dose of 1.5 mg of dexamethasone corresponded to an equivalent dose of 3.33.

In our study, denosumab, an osteoporosis medication, was administered subcutaneously at a dosage of 60 mg/mL at 6 month intervals. All patients had been receiving denosumab for a minimum of 2 years. In Group 1 patients continued their denosumab treatment while undergoing ESI therapy.

Patients Demographics

Patient age, gender, serum calcium, vitamin D levels, and phosphorus levels were recorded. The number of ESIs, along with the equivalent dose, was used to calculate the cumulative dose. Changes in patients' BMD were then monitored and analyzed.

Epidural Steroid Injectate

For each ESI, the administration procedure was as follows:

The corticosteroid used was dexamethasone 1 mg/mL. This was combined with 2% lidocaine 400 mg/20 mL (2 mL) and normal saline 7 mL, resulting in a total 10 mL solution. The injection was administered using a 10 mL syringe. We opted for lidocaine due to its relatively short half life compared to bupivacaine or ropivacaine. For dexamethasone, the choice of a nonparticulate formulation was made since it dissolves completely in water, resulting in fewer adverse effects. This formulation was selected for injection due to its reduced potential for adverse effects (13).

Statistical Analysis

An Analysis of Variance (ANOVA) test was used to compare the 3 groups. A *P* value less than 0.05 was considered to be statistically significant. IBM SPSS Statistics 23.0 (IBM Corp.) was used for data analysis.

RESULTS

In Group One, (ESI with denosumab), the mean (SD) age of patients was 71.73 (9.59) years. The men-to-women ratio was 1:39. The average vitamin D level was 24.53 ng/mL, the average calcium level was 9.183 mg/dL, and the average phosphorus level was 3.68 mg/dL.

Among the patients, 33 had received ESIs fewer than 10 times annually, while 7 had received ESIs more than 10 times. The cumulative steroid usage was converted to an equivalent dose of 18.33, roughly equivalent to 5.50 ampules (27.5 mg) of dexamethasone. Initial BMD measurements were observed as 0.811 g/cm² in the lumbar spine and 0.696 g/cm² in the hip.

In Group 2 (ESI only), patients had an average (SD) age of 70.00 (9.82) years. The men-to-women ratio was 2:33. The average vitamin D level was 26.15 ng/mL, the average calcium level was 9.180 mg/dL, and the average phosphorus level was 3.61 mg/dL. Among the patients, 31 had received ESIs fewer than 10 times annually, while 4 received ESIs more than 10 times. The cumulative steroid usage was converted to an equivalent dose of 16.67, approximately equivalent to 5.00 ampules of dexamethasone. Initial BMD measurements were recorded as 0.831 g/cm² in the spine and 0.711 g/cm² in the hip.

In Group 3 (denosumab only), patients had an average (SD) age of 71.18 (5.64) years. The men-to-women ratio was 2:31. The average vitamin D level was 26.86 ng/mL, the average calcium level was 9.306 mg/dL, and the average phosphorus level was 3.573 mg/dL. Initial BMD measurements were observed as 0.822 g/cm² in the spine and 0.668 g/cm² in the hip (Table 1).

In Group 1, lumbar BMD exhibited a noteworthy annual increase of 0.0411 g/cm²; their hip BMD increased of 0.0047 g/cm² over the course of one year. Group 2, on the other hand, experienced a decrease in lumbar BMD of 0.0307 g/cm² within the same one-year timeframe, accompanied by a concurrent decrease in hip BMD of 0.0357 g/cm². In Group 3, lumbar BMD demonstrated a one-year increase of 0.0556 g/cm²; hip BMD increased 0.0048 g/cm² during the same period (Table 2).

In the context of a follow-up study conducted over the course of one year, when comparing initial and follow-up lumbar BMD values, notable trends were observed among the 3 groups. In Group One, there was a noteworthy increase of 5.06% in lumbar BMD, Group 2 displayed a reduction of 3.70%, and Group 3 exhibited an increase of 6.77%. We performed an ANOVA analysis in order to determine the changes in lumbar BMD. The analysis revealed statistically significant differences between Groups One and 2 (P = 0.002) and Groups 2 and 3 (P < 0.001). However, no statistically significant differences were observed between Groups One and 3 (P = 0.773).

In terms of hip BMD changes, Group One showed

Table 1. Patient demographics.

Mean (SD) age (years) 71.73 (9.59) 70.00 (9.82) 71.18 (1 vs 2) Mean (SD) (years) 1/39 2/33 2/31 Mean (SD) vitamin D level (ng/mL) 24.53 (± 11.51) 26.15 (± 11.85) 26.86 (± 9.59) Mean (SD) calcium level (mg/dL) 9.183 (± 0.54) 9.180 (± 0.36) 9.306 (± 0.50) Mean (SD) phosphorus level (mg/dL) 3.68 (± 0.60) 3.68 (± 0.74) 3.573 (± 0.42) Steroid injection (dexamethasone 5 mg/each) 0 0.967 (2 vs 3) Fewer than 10 times (n) 7 4 Cumulative steroid usage (equivalent dosage) 18.33 (16.67 0 Initial bone marrow density (BMD) -2.478 (0.81) (0.831) (0.822) Hip BMD (T-score [g/cm²]) (0.696) (0.711) (0.668) -2.28 (0.267 denosumab injection (vears) Mean (SD) denosumab injection (vears) 0.696 (0.711) (0.648)		Group One (n = 40)	Group 2 (n = 35)	Group 3 (n = 33)	P Value
Mean (SD) age (years) 71.73 (9.59) 70.00 (9.82) 71.18 (1 vs 3) 0.962 (1 vs 3) Men/Women 1/39 2/33 2/31 0.840 (2 vs 3) Mean (SD) vitamin D level (ng/mL) 24.53 (±11.51) 26.15 (±11.85) 26.86 (±9.59) 0.703 (1 vs 2) Mean (SD) calcium level (mg/dL) 9.183 (±0.54) 9.180 (±0.36) 9.306 (±0.50) 0.514 (1 vs 3) Mean (SD) phosphorus level (mg/dL) 3.68 (±0.60) 3.68 (±0.74) 3.573 (±0.42) 0.729 (1 vs 3) Steroid injection (dexamethasone 5 mg/each) 0 0 0 0.967 (2 vs 3) Fewer than 10 times (n) 7 4 0 0 0.967 (2 vs 3) Lumbar BMD (T-score [g/cm²]) -2.478 (0.81) (0.831) (0.822) -2.312 (0.822) 0.865 (1 vs 2) Hip BMD (T-score [g/cm²]) -2.038 (0.696) (0.711) (0.668) -2.28 (0.267 (0.433) (1 vs 3) 0.267 (0.433) (1 vs 3)					
(years) (9.59) (9.82) (5.64) (1 vs 3) Men/Women 1/39 2/33 2/31 Mean (SD) vitamin D level (ng/mL) 24.53 (± 11.51) 26.15 (± 11.85) 26.86 (± 9.59) Mean (SD) calcium level (mg/dL) 9.183 (± 0.54) 9.180 (± 0.36) 9.306 (± 0.50) Mean (SD) phosphorus level (mg/dL) 3.68 (± 0.60) 3.61 (± 0.74) 3.573 (± 0.42) Steroid injection (dexamethasone 5 mg/each) 0 0 0.967 (2 vs 3) Fewer than 10 times (n) 7 4 0 Cumulative steroid usage (equivalent dosage) 18.33 (16.67) 0 0 Initial bone marrow density (BMD) -2.478 (0.81) (0.82) -2.274 (0.82) -2.312 (0.668) Hip BMD (T-score [g/cm²]) -2.038 (0.96) (0.711) (0.668) -2.28 (0.267 (0.433) (1 vs 3)					
Men/Women 1/39 2/33 2/31 Mean (SD) vitamin D level (ng/mL) 24.53 (± 11.51) 26.15 (± 11.85) 26.86 (± 9.59) 0.703 (1 vs 3) Mean (SD) calcium level (mg/dL) 9.183 (± 0.54) 9.180 (± 0.36) 9.306 (± 0.50) 0.514 (1 vs 3) Mean (SD) phosphorus level (mg/dL) 3.68 (± 0.60) 3.61 (± 0.74) 3.573 (± 0.42) 0.729 (1 vs 3) Steroid injection (dexamethasone 5 mg/each) 3 (± 0.74) 0.967 (2 vs 3) Fewer than 10 times (n) 7 4 4 Cumulative steroid usage (equivalent dosage) 18.33 16.67 0 0 Initial bone marrow density (BMD) 18.33 (0.83) (0.82) 1.981 (0.82) Hip BMD (T-score [g/cm²]) -2.478 (0.811) (0.831) (0.822) -2.3 (0.668) Mean (SD) duration of duration of denosumab (0.583) 2.28 (0.267 (0.433) (1 vs 3)					
Men/Women 1/39 2/33 2/31 Mean (SD) vitamin D level (ng/mL) 24.53 (± 11.51) 26.15 (± 11.85) 26.86 (± 9.59) 0.855 (1 vs 2) Mean (SD) calcium level (mg/dL) 9.183 (± 0.54) 9.180 (± 0.36) 9.306 (± 0.50) 0.514 (1 vs 3) Mean (SD) phosphorus level (mg/dL) 3.68 (± 0.60) 3.61 (± 0.74) 3.573 (± 0.42) 0.729 (1 vs 3) Steroid injection (dexamethasone 5 mg/each) 3 3 31 0.967 (2 vs 3) Fewer than 10 times (n) 3 31 0.967 (2 vs 3) Cumulative steroid usage (equivalent dosage) 18.33 (16.67) 0 0 Initial bone marrow density (BMD) 10.831) (0.822) 0.822 Hip BMD (T-score [g/cm²]) -2.478 (0.811) (0.831) (0.831) (0.668) -2.38 (0.668) Mean (SD) duration of denosumab 2.425 (0.583) (0.433) (0.433) (1 vs 3)	(years)	(5.05)	(5.02)	(0.01)	
Mean (SD) vitamin D level (ng/mL) 24.53 (± 11.51) 26.15 (± 9.59) 26.86 (± 9.59) 0.703 (1 vs 2) Mean (SD) calcium level (mg/dL) 9.183 (± 0.54) 9.180 (± 0.36) 9.306 (± 0.50) 1.000 (1 vs 2) Mean (SD) calcium level (mg/dL) 9.183 (± 0.54) 9.180 (± 0.36) 9.306 (± 0.50) 0.514 (1 vs 3) Mean (SD) phosphorus level (mg/dL) 3.68 (± 0.60) 3.61 (± 0.74) 3.573 (± 0.42) 0.729 (1 vs 3) Steroid injection (dexamethasone 5 mg/each) 0 0 0 0.967 (2 vs 3) - More than 10 times (n) 7 4 4 0 0 - Cumulative steroid usage (equivalent dosage) 18.33 (0.66) 16.67 (0.81) 0 0 0 Initial bone marrow density (BMD) 1.2478 (0.811) (0.831) (0.822) -2.312 (0.822) 0.267 (0.668) 0.267 (0.668) Hip BMD (T-score [g/cm²]) 0.696) (0.711) (0.668) 0.267 (0.668) 0.267 (0.668) 0.267 (0.668)					
Mean (SD) vitamin D level (ng/mL) 24.53 (± 11.51) 26.15 (± 11.85) 26.86 (± 9.59) 0.703 (1 vs 3) Mean (SD) calcium level (mg/dL) 9.183 (± 0.54) 9.180 (± 0.36) 9.306 (± 0.50) 1.000 (1 vs 2) Mean (SD) phosphorus level (mg/dL) 3.68 (± 0.60) 3.61 (± 0.74) 3.573 (± 0.42) 0.729 (1 vs 3) Steroid injection (dexamethasone 5 mg/each) 3 3 31 0.967 (2 vs 3) Fewer than 10 times (n) 7 4 4 0 Cumulative steroid usage (equivalent dosage) 18.33 16.67 0 0 0 Initial bone marrow density (BMD) -2.478 (0.811) (0.831) (0.831) (0.822) -2.274 (-2.312 (0.822) -2.312 (0.668) Hip BMD (T-score [g/cm²]) -2.038 (0.696) (0.711) (0.668) -1.981 (-2.3 (0.668) -2.28 (0.267 (denosumab) (0.583) (0.433) (1 vs 3)	Men/Women	1/39	2/33	2/31	
vitamin D level (ng/mL) 24.53 (± 11.51) 26.15 (± 9.59) 26.86 (1 vs 3) Mean (SD) calcium level (mg/dL) 9.183 (± 0.54) 9.180 (± 0.36) 9.306 (± 0.50) 0.514 (1 vs 3) Mean (SD) phosphorus level (mg/dL) 3.68 (± 0.60) 3.61 (± 0.74) 3.573 (± 0.729 (1 vs 3) 0.729 (1 vs 3) Steroid injection (dexamethasone 5 mg/each) 0 0 0 0 Fewer than 10 times (n) 7 4 0 0 Cumulative steroid usage (equivalent dosage) 18.33 (16.67) 0 0 0 Initial bone marrow density (BMD) 1.2478 (0.831) -2.274 (0.822) -2.312 (0.822) Hip BMD (T-score [g/cm²]) -2.038 (0.696) -1.981 (0.822) -2.3 (0.668) Mean (SD) duration of denosumab 2.425 (0.583) 2.28 (0.433) (1 vs 3)					
Mean (SD) 9.183 9.180 (± 0.50) (1 vs 2) 0.514 (1 vs 3) 0.521 (2 vs 3) (2 vs 3) 0.521 (2 vs 3) (2 v	` ′				
Mean (SD) calcium level (mg/dL) 9.183 (± 0.54) 9.180 (± 0.36) 9.306 (± 0.50) 0.514 (1 vs 2) Mean (SD) phosphorus level (mg/dL) 3.68 (± 0.60) 3.61 (± 0.74) 3.573 (± 0.42) 0.729 (1 vs 3) Steroid injection (dexamethasone 5 mg/each) 0 0 0 0 0.967 (2 vs 3) Fewer than 10 times (n) 7 4 4 0 0 0 0 Cumulative steroid usage (equivalent dosage) 18.33 (0.81) (0.831) (0.831) (0.822) 16.67 (0.822) 0 0 0 0 0 Hip BMD (T-score [g/cm²]) -2.478 (0.811) (0.831) (0.831) (0.668) (0.711) (0.668) -2.3 (0.668) (0.711) (0.668) 0 <td>(ng/mL)</td> <td>(± 11.51)</td> <td>(± 11.85)</td> <td>(± 9.59)</td> <td>, ,</td>	(ng/mL)	(± 11.51)	(± 11.85)	(± 9.59)	, ,
Mean (SD) calcium level (mg/dL) 9.183 (± 0.54) 9.180 (± 0.36) 9.306 (± 0.50) 0.514 (1 vs 3) Mean (SD) phosphorus level (mg/dL) 3.68 (± 0.60) 3.61 (± 0.74) 3.573 (± 0.42) 0.729 (1 vs 3) Steroid injection (dexamethasone 5 mg/each) 0 0 0.967 (2 vs 3) Fewer than 10 times (n) 7 4 0 Cumulative steroid usage (equivalent dosage) 18.33 (0.831) 16.67 (0.822) 0 Initial bone marrow density (BMD) 1.981 (0.822) -2.312 (0.822) Hip BMD (T-score [g/cm²]) -2.038 (0.696) (0.711) (0.668) -2.28 (0.667) (0.433) (1 vs 3) Mean (SD) duration of denosumab (0.583) 2.228 (0.433) (1 vs 3)					
Mean (SD) calcium level (mg/dL) 9.183 (± 0.54) 9.180 (± 0.36) 9.306 (± 0.50) 0.514 (1 vs 3) Mean (SD) phosphorus level (mg/dL) 3.68 (± 0.60) 3.61 (± 0.74) 3.573 (± 0.42) 0.729 (1 vs 3) Steroid injection (dexamethasone 5 mg/each) 0 0 0 0 Fewer than 10 times (n) 7 4 0 Cumulative steroid usage (equivalent dosage) 18.33 (16.67) 0 0 Initial bone marrow density (BMD) -2.478 (-2.274 (0.811) (0.831) (0.822) -2.312 (0.822) Hip BMD (T-score [g/cm²]) (0.696) (0.711) (0.668) -2.38 (0.668) (0.711) (0.668) -2.28 (0.267 (1 vs 3) (1 vs 3) Mean (SD) duration of denosumab (0.583) 2.28 (0.433) (1 vs 3) 0.267 (1 vs 3)					
Calcium level (mg/dL)	l ` ′	9.183	9.180	9.306	
Mean (SD) phosphorus level (mg/dL) 3.68 (± 0.60) 3.61 (± 0.74) 3.573 (± 0.42) 0.729 (1 vs 3) Steroid injection (dexamethasone 5 mg/each) 0 0 0 0.967 (2 vs 3) Fewer than 10 times (n) 7 4 4 0 Cumulative steroid usage (equivalent dosage) 18.33 (0.81) (0.822) 16.67 (0.811) (0.831) (0.822) 0 Lumbar BMD (T-score [g/cm²]) -2.478 (0.811) (0.831) (0.822) -2.312 (0.822) 0.267 (0.711) (0.668) Mean (SD) duration of denosumab (0.583) 2.28 (0.433) (1 vs 3) 0.267 (1 vs 3)					
Mean (SD) phosphorus level (mg/dL) 3.68 (± 0.60) 3.61 (± 0.74) 3.573 (± 0.42) 0.729 (1 vs 3) Steroid injection (dexamethasone 5 mg/each) 0 0 0.967 (2 vs 3) Fewer than 10 times (n) 33 31 31 - More than 10 times (n) 7 4 4 Cumulative steroid usage (equivalent dosage) 18.33 16.67 0 Initial bone marrow density (BMD) Lumbar BMD (T-score [g/cm²]) -2.478 (0.811) (0.831) (0.822) -2.312 (0.822) Hip BMD (T-score [g/cm²]) -2.038 (0.696) (0.711) (0.668) -2.3 (0.668) Mean (SD) duration of denosumab (0.583) 2.28 (0.267 (1 vs 3))	(mg/uz)				
Mean (SD) phosphorus level (mg/dL) 3.68 (± 0.60) 3.61 (± 0.74) 3.573 (± 0.42) 0.729 (1 vs 3) Steroid injection (dexamethasone 5 mg/each) 0 0 0.967 (2 vs 3) Fewer than 10 times (n) 33 31 31 - More than 10 times (n) 7 4 4 Cumulative steroid usage (equivalent dosage) 18.33 16.67 0 0 Initial bone marrow density (BMD) Lumbar BMD (T-score [g/cm²]) -2.478 (0.81) (0.831) (0.822) -2.312 (0.822) Hip BMD (T-score [g/cm²]) -2.038 (0.696) (0.711) (0.668) -2.3 (0.668) Mean (SD) duration of denosumab (0.583) 2.28 (0.433) (1 vs 3)					0.865
Steroid injection (dexamethasone 5 mg/each)	Moon (SD)				(1 vs 2)
Steroid injection (dexamethasone 5 mg/each)					
Steroid injection (dexamethasone 5 mg/each)	(mg/dL)	(± 0.00)	(± 0.74)	(± 0.42)	
(dexamethasone 5 mg/each) 0 Fewer than 10 times (n) 33 - More than 10 times (n) 7 4 4 Cumulative steroid usage (equivalent dosage) 18.33 16.67 0 Initial bone marrow density (BMD) Lumbar BMD (T-score [g/cm²]) -2.478 (0.811) (0.831) (0.822) -2.312 (0.822) Hip BMD (T-score [g/cm²]) -2.038 (0.696) (0.711) (0.668) -2.3 (0.668) Mean (SD) duration of denosumab (0.583) 2.28 (0.267 (1 vs 3))					
times (n) - More than 10 times (n) Cumulative steroid usage (equivalent dosage) Initial bone marrow density (BMD) Lumbar BMD	(dexamethasone			0	
times (n) Cumulative steroid usage (equivalent dosage) Initial bone marrow density (BMD) Lumbar BMD (T-score [g/cm²]) Hip BMD -2.038 -1.981 (T-score [g/cm²]) (0.696) Mean (SD) duration of denosumab (0.583) 2.28 0.267 denosumab 4 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0		33	31		
Steroid usage (equivalent dosage) 18.33 16.67 0		7	4		
Lumbar BMD (T-score [g/cm²]) -2.478 (0.811) -2.274 (0.831) -2.312 (0.822) Hip BMD (T-score [g/cm²]) -2.038 (0.696) -1.981 (0.711) -2.3 (0.668) Mean (SD) duration of denosumab 2.425 (0.583) 2.28 (0.433) 0.267 (1 vs 3)	steroid usage (equivalent	18.33	16.67	0	
(T-score [g/cm²]) (0.811) (0.831) (0.822) Hip BMD (T-score [g/cm²]) -2.038 (0.696) -1.981 (0.711) -2.3 (0.668) Mean (SD) duration of denosumab 2.425 (0.583) 2.28 (0.433) 0.267 (1 vs 3)	Initial bone marrow density (BMD)				
(T-score [g/cm²]) (0.811) (0.831) (0.822) Hip BMD (T-score [g/cm²]) -2.038 (0.696) -1.981 (0.711) -2.3 (0.668) Mean (SD) duration of denosumab 2.425 (0.583) 2.28 (0.433) 0.267 (1 vs 3)	Lumbar BMD	-2.478	-2.274	-2.312	
(T-score [g/cm²]) (0.696) (0.711) (0.668) Mean (SD) duration of 2.425 2.28 0.267 denosumab (0.583) (0.433) (1 vs 3)					
Mean (SD) 2.425 2.28 0.267 denosumab (0.583) (0.433) (1 vs 3)	1 -				
duration of denosumab 2.425 (0.583) 2.28 (0.267 (1 vs 3))		(((
	duration of				
	denosumab injection (years)	(0.583)		(0.433)	(1 vs 3)

Group 1: Patients who received an epidural steroid injection and denosumab.

Group 2: Patients who only received an epidural steroid injection.

Group 3: Patients who only received denosumab.

an increase of 0.68%, Group 2 showed a reduction of 5.02%, and Group 3 showed an increase of 0.69%. Similar to the lumbar analysis, ANOVA was applied to evaluate hip BMD changes, which revealed statistically significant differences between Groups One and 2 (P = 0.003) and Groups 2 and 3 (P < 0.001). However, no statistically significant differences were observed between Groups One and 3 (P = 0.858) (Table 3, Fig 1.).

Furthermore, there were no statistically significant differences observed among the 3 groups in terms of age, vitamin D levels, calcium levels, and phosphorus levels.

DISCUSSION

Previous studies have reported an increased risk of fractures associated with corticosteroid use (14). Additionally, the same trend has been observed in several studies of ESIs. The heightened risk of fractures is attributed to the effect of steroids on BMD, a phenomenon that can be explained by the mechanism of action of steroids. Steroids increase the expression of RANKL, a cytokine that enhances the differentiation and activation of osteoclasts, resulting in a decrease in BMD.

According to van Staa's research (3), a study involving daily oral administration of a low dose of 2.5 mg prednisone, a significant reduction of approximately

Table 2. Bone mineral density (BMD) change.

	Group One	Group 2	Group 3
Lumbar BMD	+ 0.0411	- 0.0307	+ 0.0556
change (g/cm²[%])	(5.06)	(3.70)	(6.77)
Hip BMD change (g/cm²[%])	+ 0.0047	-0.0357	+ 0.0048
	(0.68)	(5.02)	(0.69)

Group 1: Patients who received an epidural steroid injection and denosumab.

Group 2: Patients who only received an epidural steroid injection.

Group 3: Patients who only received denosumab.

Table 3. Bone marrow density change analysis.

	Group	Versus Group	P value
Lumbar BMD change (g/cm²)	One	2	0.002
		3	0.773
	2	3	< 0.001
Hip BMD change (g/cm²)	One	2	0.003
		3	0.858
	2	3	< 0.001

Group 1: Patients who received an epidural steroid injection and denosumab. $\,$

Group 2: Patients who only received an epidural steroid injection.

Group 3: Patients who only received denosumab.

8% in BMD was shown at a follow-up period of 5 months. Additionally, the study revealed a positive correlation between increasing steroid dosage and the extent of BMD decrease (3). A similar trend of decreased BMD has been observed in our patients receiving ESIs, where the systemic effect is generally expected to be lower in patients who received an epidural steroid injection compared to those who continuously took oral steroids

In our study, patients in Group 2 underwent ESIs with an equivalent dose of 16.67 for a year, which corresponds to about 25 mg/y of dexamethasone. Previously, the effect of epidural steroids on BMD was inconsistent; the effect depended on the type of epidural steroid and the study patients. However, our study revealed clearly that when 25 mg of dexamethasone was injected through the epidural route over a year's time, lumbar spine BMD significantly decreased by 3% and femoral neck BMD decreased by 5% in patients with osteoporosis who were on average 70 years old. Similarly, Kim, et al (7) reported 52 women who were postmenopausal (average age 67) showed an average decline in hip BMD of 2.23% after receiving an ESI containing 8.94 mg of dexamethasone over a mean period of 16 months. Considering this and a previous study (7) about epidural dexamethasone's effect on BMD, it appears that an ESI containing dexamethasone would

accelerate the decrease of BMD in elderly patients with osteoporosis.

According to Vydra et al (15), 10 mg of dexamethasone was favored by the majority of doctors (56%) for ESIs, with 8 mg coming in second (12%) in their survey. Additionally, many of the doctors (40%) permitted 4 ESIs every year, followed by 3 (29%), and 6 (17%) (15). In our study, the amount of epidural dexamethasone administered per patient in Group 2 was on average 5 ampules, which means that ESIs were performed about 5 times a year, considering that one ample was used per single injection. Therefore, considering the actual clinical survey results mentioned above, 5 ESIs containing dexamethasone per year are common; however, elderly patients with osteoporosis can have a decrease in BMD when they undergo ESIs. Kim, et al (7) documented that an epidural steroid injection with 9.73 mg of dexamethasone for a mean period of 15 months, administered to patients receiving risedronate, ibandronate, or alendronate, resulted in approximately a 1%-2% increase in lumbar spine BMD (7). In contrast, patients using selective estrogen receptor modulators and calcium and vitamin D agents, exhibited a trend of approximately a 2% reduction in lumbar BMD. However, there are no reports regarding the effect of steroid injections on BMD in patients using denosumab (16).

The mechanism of action of bisphosphonates

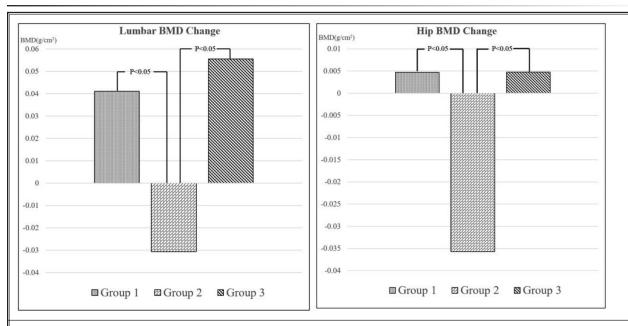


Fig. 1. Lumbar and hip bone mineral density change from baseline to one-year follow-up. Group 1: epidural steroid injection (ESI) with denosumab; Group 2: ESI only; Group 3: denosumab only.

www.painphysicianjournal.com E187

and denosumab offers insight into their differential effects in the context of steroid-induced osteoporosis. Nitrogen-containing bisphosphonates function by inhibiting farnesyl pyrophosphate synthase, a key enzyme involved in the attachment of osteoclasts to the bone matrix. This disruption leads to the detachment of osteoclasts from the bone surface, effectively reducing bone resorption and mitigating the decline in BMD (17,18). On the other hand, denosumab acts as a competitive inhibitor of RANKL, operating more directly on the steroid's mechanism of osteoclast activation. As a result, denosumab can reduce the effect of steroids on BMD by inhibiting osteoclast activation more effectively.

Based on the actual analysis results, it can be asserted that patients receiving denosumab exhibited a notable increase of 6.77% in lumbar BMD and 0.69% in hip BMD, surpassing the modest 1%–2% BMD increase typically observed with bisphosphonate formulations. Furthermore, our study indicates that denosumab demonstrated a significant difference, with a 5.06% increase in lumbar BMD and a 0.68% increase in hip BMD.

Consequently, it can be inferred that the utilization of denosumab in patients undergoing an ESI provides greater benefits in preventing the exacerbation of osteoporosis compared to patients who do not take denosumab. Moreover, guided by our study's findings, it can be deduced that administering an annual average of 25 mg of dexamethasone via epidural injection to patients with osteoporosis who also receive denosumab would have a limited adverse effect on lumbar BMD.

Limitations

The number of patients recruited in our study was relatively small and limited to specific age groups. The group that received ESIs used, on average, 25 mg of dexamethasone annually. However, it was challenging to obtain more significant findings about the frequency of injections because of the small number of patients. Therefore, based on these results, further analysis with a larger patient population is necessary to examine the relationship between the number of ESIs and BMD. Nonetheless, the patients in our study matched well demographically across groups, and while a specific age group was enrolled, the group of patients frequently encountered in clinical practice was chosen.

Due to the retrospective nature of our study, another limitation was the lack of assessment and analysis of bone turnover markers including PTH, osteocalcin, N-terminal propeptide of type 1 procollagen (P1NP), C-telopeptide of Collagen Type 1 (CTx), N-telopeptide of Collagen Type 1 (NTx), and deoxypyridinoline. In addition, as a retrospective study, there may be neglect regarding smoking status or details of medications being taken by the study patients. Based on these clinical findings, further studies with a larger patient cohort are needed to perform a more comprehensive analysis, including bone turnover markers and detailed patient factors, such as the use of bone metabolism-related medications.

Conclusion

The propensity of glucocorticoids to accelerate the development of osteoporosis is widely acknowledged. Our study also shows that local ESIs of dexamethasone reduce BMD in elderly patients with osteoporosis. However, when denosumab is administered to patients with osteoporosis who are receiving dexamethasone-based ESIs, the steroid did not exhibit a significant effect on BMD. Particularly noteworthy is the observation that utilizing spinal ESIs may not contribute to an expedited decline in lumbar BMD in patients undergoing denosumab therapy.

REFERENCES

- Carassiti M, Pascarella G, Strumia A, et al. Epidural steroid injections for low back pain: A narrative review. Int J Environ Res Public Health 2021; 19:231...
- Overman RA, Toliver JC, Yeh JY, Gourlay ML, Deal CL. United States adults meeting 2010 American College of Rheumatology criteria for treatment and prevention of glucocorticoidinduced osteoporosis. Arthritis Care Res
- (Hoboken) 2014; 66:1644-1652.
- Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. *J Bone Miner Res* 2000; 15:993-1000.
- Manchikanti L, Pampati V, Beyer C, Damron K, Cash K, Moss T. The effect of neuraxial steroids on weight and bone mass density: A prospective evaluation. Pain Physician 2000; 3:357-366.
- Dubois EF, Wagemans MF, Verdouw BC, et al. Lack of relationships between cumulative methylprednisolone dose and bone mineral density in healthy men and postmenopausal women with chronic low back pain. Clin Rheumatol 2003; 22:12-17.
- Kang SS, Hwang BM, Son H, Cheong IY, Lee SJ, Chung TY. Changes in bone mineral density in postmenopausal

- women treated with epidural steroid injections for lower back pain. *Pain Physician* 2012; 15:229-236.
- Kim S, Hwang B. Relationship between bone mineral density and the frequent administration of epidural steroid injections in postmenopausal women with low back pain. *Pain Res Manag* 2014; 19:30-34.
- Kang WY, Lee JW, Lee E, Kang Y, Ahn JM, Kang HS. Systemic effects of fluoroscopically guided epidural steroid injection with dexamethasone. Korean J Pain 2019; 32:178-186.
- Yanbeiy ZA, Hansen KE. Denosumab in the treatment of glucocorticoidinduced osteoporosis: A systematic review and meta-analysis. *Drug Des Devel Ther* 2019; 13:2843-2852.
- 10. Kanis JA. Assessment of fracture risk and its application to screening for

- postmenopausal osteoporosis: Synopsis of a WHO report. *Osteoporos Int* 1994; 4:368-381.
- II. Kanis J, Glüer C-C; Committee of Scientific Advisors IOF. An update on the diagnosis and assessment of osteoporosis with densitometry. Osteoporos Int 2000; 11:192-202.
- Lee JH. The understanding and appropriate use of corticosteroid in epidural injection: A narrative review. Int J Pain 2024; 15:80-87.
- MacMahon PJ, Huang AJ, Palmer WE. Spine Injectables: What is the safest cocktail? AJR Am J Roentgenol 2016; 207:526-53.
- 14. Kerezoudis P, Rinaldo L, Alvi MA, et al. The effect of epidural steroid injections on bone mineral density and vertebral fracture risk: A systematic review and critical appraisal of current literature.

- Pain Med 2018; 19:569-579.
- Vydra D, McCormick Z, Clements N, Nagpal A, Julia J, Cushman D. Current trends in steroid dose choice and frequency of administration of epidural steroid injections: A survey study. PM R 2020; 12:49-54.
- 16. Kim YU, Karm MH, Cheong Y, et al. Effect of epidural steroid injection on bone mineral density in postmenopausal women according to antiosteoporotic medication use. *Pain Physician* 2016; 19:389-396.
- Allen CS, Yeung JH, Vandermeer B, Homik J. Bisphosphonates for steroidinduced osteoporosis. Cochrane Database Syst Rev 2016; 10:CD001347.
- Drake MT, Clarke BL, Khosla S. Bisphosphonates: Mechanism of action and role in clinical practice. Mayo Clin Proc 2008; 83:1032-1045.

www.painphysicianjournal.com E189