Early Initiation of Bisphosphonate Does Not Affect Healing and Outcomes of Volar Plate Fixation of Osteoporotic Distal Radial Fractures

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Background: Bisphosphonates can adversely affect fracture-healing because they inhibit osteoclastic bone resorption. It is unclear whether bisphosphonates can be initiated safely for patients who have sustained an acute distal radial fracture. The purpose of this randomized study was to determine whether the early use of bisphosphonate affects healing and outcomes of osteoporotic distal radial fractures treated with volar locking plate fixation.

Methods: Fifty women older than fifty years of age who had undergone volar locking plate fixation of a distal radial fracture and had been diagnosed with osteoporosis were randomized to Group I (n = 24, initiation of bisphosphonate treatment at two weeks after the operation) or Group II (n = 26, initiation of bisphosphonate treatment at three months). Patients were assessed for radiographic union and other radiographic parameters (radial inclination, radial length, and volar tilt) at two, six, ten, sixteen, and twenty-four weeks, and for clinical outcomes that included Disabilities of the Arm, Shoulder and Hand (DASH) scores, wrist motion, and grip strength at twenty-four weeks. The two groups were compared with regard to the time to radiographic union, the radiographic parameters, and the clinical outcomes.

Results: No significant differences were observed between the two groups with respect to radiographic or clinical outcomes after volar locking plate fixation. All patients obtained fracture union, and the mean times to radiographic union in Groups I and II were similar (6.7 and 6.8 weeks, respectively; p = 0.65). Furthermore, the time to radiographic union was not related to osteoporosis severity or fracture type.

Conclusions: In patients with an osteoporotic distal radial fracture treated with volar locking plate fixation, the early initiation of bisphosphonate treatment did not affect fracture-healing or clinical outcomes.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

Disclosure: None of the authors received payments or services, either directly or indirectly (i.e., via his or her institution), from a third party in support of any aspect of this work. None of the authors, or their institution(s), have had any financial relationship, in the thirty-six months prior to submission of this work, with any entity in the biomedical arena that could be perceived to influence or have the potential to influence what is written in this work. Also, no author has had any other relationships, or has engaged in any other activities, that could be perceived to influence or have the potential to influence what is written in this work. The complete Disclosures of Potential Conflicts of Interest submitted by authors are always provided with the online version of the article.
Distal radial fractures are the most common fractures encountered in the upper extremity and represent a public health concern, particularly in the elderly. Middle-aged and elderly patients with a distal radial fracture have a higher risk of subsequent fractures than those with no previous fracture. Furthermore, patients with a distal radial fracture are an average of fifteen years younger than those with a hip fracture. Therefore, patients with a distal radial fracture offer physicians an important opportunity to start preventative treatment for osteoporosis. However, many authors have reported low rates of osteoporosis evaluation and treatment in patients with a distal radial fracture. To improve this care gap, Rozental et al. showed that simply ordering a bone mineral density examination in an orthopaedic clinic improves osteoporosis treatment rates by primary physicians after a distal radial fracture. In addition, faxing or sending electronic reminders concerning treatment guidelines to primary physicians regarding patients treated for a fragility fracture improves the osteoporosis treatment rate. It is possible that the osteoporosis treatment rate may increase if the intervention can start immediately after the diagnosis of a fracture.

Bisphosphonates are the most commonly used osteoporosis medication, and their mode of action involves the inhibition of osteoclastic bone resorption. Since fracture-healing involves callus remodeling, it has been hypothesized that bisphosphonates can prevent healing, or even accelerated healing. However, studies on the subject have produced contradictory results, with various authors reporting delays in healing, no effects, or even accelerated healing. These diverse results appear to be due to the different fracture models, different bisphosphonates, and different fracture fixation methods used. In a study of the treatment of distal radial fractures, Rozental et al. reported a delay in union time of less than one week for patients taking bisphosphonates as compared with non-treated controls. However, their study was retrospective with differences in the timing of radiographic examinations, and they included nonsurgically treated patients and patients who were already taking a bisphosphonate at the time of injury. In addition, osteoporosis status was not determined in the controls, so it is unclear when bisphosphonate medication can be initiated safely for those with a new distal radial fracture.

Recently, open reduction and internal fixation with a volar locking plate has become a popular option for the treatment of unstable distal radial fractures because it provides stable fixation and allows early wrist motion. We hypothesized that the early initiation of bisphosphonate treatment for patients treated with a volar locking plate fixation system would not affect fracture-healing or clinical outcomes. The purpose of this randomized, prospective study was to determine whether the early use of bisphosphonate affects healing and outcomes of osteoporotic distal radial fractures treated with volar locking plate fixation.

### Materials and Methods

#### Study Population

Ethics Committee/Human Studies Committee approval was obtained for this study. The Seoul National University Bundang Hospital's clinical trial registry number was B-1107/131-001.

Beginning in January 2007, all women older than fifty years of age presenting at our institution (an urban tertiary referral hospital for trauma) with a distal radial fracture caused by minor trauma, such as a fall on an outstretched hand, were recommended for bone mineral density examinations unless they had already undergone the examination or were already being treated for osteoporosis. Dual x-ray absorptiometry (DXA) scans (Lunar Prodigy; GE Lunar, Madison, Wisconsin) were performed on all eligible patients within two weeks after the fracture. Those who were treated with a volar locking plate and had a femoral neck or spine T score of ≤−2.5 for the first time were approached regarding enrollment in this study at two weeks after surgery. The indications for the operation were (1) radial shortening of >5 mm, (2) dorsal angulation of >10° or volar angulation of >20° on lateral radiographs of the wrist, (3) radial inclination of <10° on a posteroanterior view of the wrist, and (4) an articular step-off of >2 mm on radiographs made after closed reduction or on follow-up radiographs made within one week after injury. The

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**Fig. 1**  
A CONSORT flow diagram for enrollment and analysis. Group I had initiation of bisphosphonate medication at two weeks postoperatively, and Group II had initiation of bisphosphonate medication at three months postoperatively.
study inclusion criteria were (1) an age of more than fifty years and osteoporosis as determined by femoral neck or spine bone mineral density examinations, (2) a distal radial fracture with or without an ulnar styloid fracture in which the radius was treated with volar open reduction and internal fixation with a volar locking plate but the ulna was not repaired, and (3) no requirement for additional surgery for a carpal bone injury or another injury other than the wrist injury. The exclusion criteria were (1) refusal to take or a contraindication for bisphosphonate medication; (2) a condition capable of affecting bone mineral density or bone metabolism, such as renal or adrenal insufficiency, diabetes, rheumatoid arthritis, thyroid disease, Parkinson disease, or chronic obstructive pulmonary disease, or any history of taking any medication known to affect bone mineral density, such as corticosteroids; (3) an open fracture, or a severely comminuted fracture or bone loss requiring an autogenous bone graft or bone graft substitute material; and (4) a fracture operated on more than three weeks after injury that could require osteotomy. We did not enroll those with osteopenia (a T score between $-2.5$ and $-1.0$) because only those with a T score of $\leq -2.5$ are covered for the bisphosphonate cost by the Korean national insurance program.

Patients who agreed to participate in the study were randomly allocated to either Group I (initiation of bisphosphonate medication at two weeks post-operatively) or Group II (the control group, initiation of bisphosphonate medication at three months postoperatively) with use of a computer-generated list (Fig. 1). As fractures usually heal within three months, the controls were given bisphosphonates at three months. Blinding was not possible because of the nature of the study. The patients were given 70 mg of alendronate weekly.

Initially, thirty patients were enrolled in each group, but two patients in Group I and one patient in Group II had to stop taking the alendronate medication because of gastrointestinal problems, and four patients in Group I and three in Group II were lost to follow-up. Thus, twenty-four patients in Group I and twenty-six in Group II were included in the final analysis. The authors of the present study prescribed the bisphosphonates and monitored side effects, such as gastrointestinal problems or flu-like symptoms. The two patient groups were similar in terms of age, body mass index, bone mineral density, AO fracture classification, and prevalence of ulnar styloid fracture (see Appendix).

**Surgery/Postoperative Care**

All surgical procedures were performed by one hand surgeon with use of regional or general anesthesia. At the beginning of each operation, a longitudinal incision was made on the volar side of the distal part of the forearm and the radius was approached through the sheath of the flexor carpi radialis tendon. The pronator quadratus was then elevated off its radial insertion, and the fracture was reduced and fixed with use of a volar locking plate system (Acumed, Hillsboro, Oregon). Ulnar styloid fractures, when present, were not treated surgically. No case of apparent instability of the distal radioulnar joint was encountered at the completion of the radial fixation.

Postoperatively, the wrist was immobilized with use of a short-arm volar plaster splint, and the patient was encouraged to perform active shoulder, elbow, and finger motion exercises. At one week postoperatively, all wrists were placed in a removable wrist brace. Physiotherapy and occupational therapy were started at

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**Figs. 2-A through 2-F** Radiographs for determination of fracture-healing in a sixty-eight-year-old patient with a distal radial fracture treated with a volar locking plate. **Figs. 2-A and 2-B** Preoperative anteroposterior and lateral radiographs showing a dorsally angulated distal radial fracture and an ulnar styloid fracture.
two weeks postoperatively. The brace was used for approximately six weeks as required by the patient. We recommended that the patients use a brace when outside or at night, and we encouraged them to use the wrist gradually at home within comfortable ranges. Generally, most of the patients had discarded the brace by the six-week follow-up examination.

Measures
The patients were routinely followed at two, six, ten, sixteen, and twenty-four weeks after surgery, and standard posteroanterior and lateral radiographs were obtained at each visit.

We set the primary treatment outcome as the time to radiographic union, which was defined as the time to fracture bridging by trabecular or osseous bone in at least one cortex as seen on anteroposterior radiographs and one as seen on lateral radiographs. At each follow-up visit, fracture bridging of the medial and lateral cortices was determined on anteroposterior radiographs and bridging of the dorsal cortex was determined on lateral radiographs (Figs. 2-A through 2-F). Bridging was defined as either “none” when there was no change at the cortical interruption compared with the appearance on the radiograph made immediately after surgery or “present” when a bridge was observed across the cortical interruption. As the initial fracture reduction of the volar cortex and the volar plate often interfered with the determination of cortical bridging at the volar surface, only changes at the dorsal cortex were considered on the lateral radiographs. Two orthopaedic surgeons, who were blinded to group assignments, reviewed the serial radiographs of all patients and determined the times to radiographic union. When the two reviewers had a different opinion on the fracture-union time point, they discussed this and agreed on one time point. The reviewers had six disagreements (three in each group). The longer time to radiographic union was generally selected in these cases. The Cohen kappa coefficient of the interobserver reliability for determination of fracture union was 0.516 (p < 0.001). We did not assess tenderness at the fracture site as evidence of clinical union. Radiographic parameters (radial inclination, radial length, and volar tilt) were also measured with use of a PACS (picture archiving and communication system).

Secondary outcomes were Disabilities of the Arm, Shoulder and Hand (DASH) scores at twenty-four weeks. The DASH questionnaire was administered by an independent examiner not directly involved in the care of the patients and unaware of the group assignments. This questionnaire was used to quantify general disabilities related to the upper extremity and contained thirty items: twenty-one that addressed difficulties with specific tasks, five that evaluated symptoms, and four that addressed social functions, work, sleep, and confidence. DASH scores range from 0 and 100, and higher scores indicate greater upper-extremity disability. The average DASH score for the general population has been reported to be 10 ± 15 points.

Other clinical outcomes that were measured were wrist motion and grip strength at twenty-four weeks. The first author evaluated passive ranges of wrist motion by recording flexion, extension, and pronation/supination.
using a standard goniometer, and measured grip strength using a Jamar dynamometer (Asimow Engineering, Los Angeles, California) with the patient’s elbow flexed at 90° and the forearm in neutral rotation. Strength was recorded in kilograms.

Statistical Analysis
To determine statistical power, the time to radiographic union was used as the primary outcome variable. In a previous study, the mean time to union of distal radial fractures in those taking bisphosphonates was fifty-five days and the standard deviation was seventeen days. On the basis of that study, we designed the current investigation to determine a two-week (fourteen-day) difference in the time to union between the two groups, with a standard deviation of seventeen days (an effect size of 0.8). Power analysis indicated that a sample size of twenty-four patients per group would provide 80% statistical power to detect this effect size between the groups (alpha = 0.05, beta = 0.20) with use of the Student t test.

Group results were compared by using the Pearson chi-square or Fisher exact test for categorical variables and the Student t test for continuous variables. Correlation analyses were performed to identify relationships between variables. Statistical analyses were performed with use of SPSS software (version 18.0; SPSS, Chicago, Illinois), and p values of <0.05 were considered significant.

Source of Funding
No funding was received for this study.

Results
Radiographic Outcomes
All patients had fracture-healing. In Group I, radiographic fracture union was obtained at six weeks in twenty patients (83%) and at ten weeks in four (17%). In Group II, radiographic fracture union was achieved at six weeks in twenty patients (77%) and at ten weeks in six (23%). The average times to radiographic union were similar (6.7 weeks [range, six to ten weeks]) in Group I and 6.8 weeks [range, six to ten weeks] in Group II; (p = 0.65). There was no significant difference in the proportion of patients who obtained healing at six weeks between the groups (p = 0.81). Radiographic parameters measured at twenty-four weeks are presented in Table I. No significant intergroup difference was evident.

Clinical Outcomes
At twenty-four weeks, the DASH scores averaged 17 points (range, 0 to 46 points) in Group I and 15 points (range, 0 to 45 points) in Group II. No significant difference was observed between the mean DASH scores of the two groups (p = 0.61). In addition, wrist motion and grip strength did not differ significantly between the groups (Table I).
**Correlation Between Variables**

When all patients in both groups were analyzed, a strong negative correlation was found between age and bone mineral density in the femoral neck ($r = -0.612$, $p < 0.001$) and the lumbar spine ($r = -0.826$, $p < 0.001$). However, the fracture type, which possibly represents severity of comminution and stability, was not associated with bone mineral density in the femoral neck ($p = 0.335$) or the lumbar spine ($p = 0.71$). Furthermore, the time to radiographic fracture union was not related to osteoporosis severity ($p = 0.513$ for femoral neck bone mineral density and $p = 0.424$ for lumbar bone mineral density) or fracture type ($p = 0.41$). Similar results were found when the two groups were analyzed separately.

**Complications**

No case of neuropathy, infection, stiffness of the hand, or complex regional pain syndrome was encountered. Two patients in Group I and one patient in Group II developed adhesive capsulitis of the shoulder. Five patients in Group I and eight in Group II requested implant removal and were operated on after study completion. One eighty-two-year-old, previously healthy patient in Group II developed postoperative capsulitis of the shoulder. Five patients in Group I and eight patients in Group II developed adhesive capsulitis of the shoulder. Two patients in Group I and one patient in Group II developed adhesive capsulitis of the shoulder. All patients in Group II requested implant removal and were operated on after study completion.

**Discussion**

It has been unclear whether bisphosphonate therapy can be initiated safely for a patient who has sustained an acute distal radial fracture. This randomized clinical trial demonstrates that initiation of bisphosphonate treatment two weeks after stable fixation of an osteoporotic distal radial fracture with the volar locking plate system does not affect the time to radiographic fracture union, other radiographic outcomes, or clinical outcomes (the DASH score, wrist motion, and grip strength). Our findings suggest that osteoporosis medication can be initiated early after stable fracture fixation in those at high risk of future fracture. The rate of osteoporosis treatment, which is still low in patients with a distal radial fracture, may increase if the treating orthopaedic surgeon can start it immediately after fracture fixation, and many studies have suggested the benefits of early intervention in patients who have experienced a fragility fracture.

Several animal studies have demonstrated that bisphosphonate can delay fracture-healing, and the authors have attributed this to delayed callus remodeling. Clinically, Odvina et al. observed significantly delayed healing of nonspinal fractures in patients on long-term alendronate, and Rozental et al. reported a less than one-week delay in distal radial fracture healing times in patients who had taken bisphosphonates for an average of twenty-five months as compared with patients who had not taken bisphosphonates. However, the authors of these clinical studies did not evaluate the effect of initiating bisphosphonate medication on fracture-healing in patients who had no history of taking bisphosphonates.

In contrast, several authors have reported that bisphosphonates promote fracture repair. Amanat et al. demonstrated that a single dose of zoledronic acid significantly increased callus volume and mechanical strength. Fleisch pointed out that, in the majority of animal studies, callus size either was not influenced or was increased by bisphosphonates and it never decreased due to the slowing of callus resorption. Furthermore, this resulted in a paradoxical increase in mechanical strength in some studies. Therefore, it seems that, although complete fracture-healing including remodeling can be delayed by the

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**TABLE I Radiographic and Clinical Outcomes at Twenty-four Weeks Postoperatively**

<table>
<thead>
<tr>
<th></th>
<th>Group I (Started Bisphosphonates at 2 Weeks)* (N = 24)</th>
<th>Group II (Started Bisphosphonates at 3 Months)* (N = 26)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to radiographic healing</td>
<td>6.7 ± 1.5</td>
<td>6.8 ± 1.6</td>
<td>0.650</td>
</tr>
<tr>
<td>Proportion with healing at 6 weeks</td>
<td>20/24</td>
<td>20/26</td>
<td>0.814</td>
</tr>
<tr>
<td>Radiographic parameters</td>
<td></td>
<td></td>
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<tr>
<td>Radial inclination (deg)</td>
<td>20 ± 2</td>
<td>19 ± 2</td>
<td>0.211</td>
</tr>
<tr>
<td>Radial length (mm)</td>
<td>10 ± 2</td>
<td>10 ± 2</td>
<td>0.883</td>
</tr>
<tr>
<td>Volar tilt (deg)</td>
<td>5 ± 4</td>
<td>6 ± 3</td>
<td>0.365</td>
</tr>
<tr>
<td>DASH scores (points)</td>
<td>17 ± 14 (range, 0-46)</td>
<td>15 ± 14 (range, 0-45)</td>
<td>0.610</td>
</tr>
<tr>
<td>Wrist ranges of motion (deg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexion</td>
<td>50 ± 10</td>
<td>51 ± 14</td>
<td>0.784</td>
</tr>
<tr>
<td>Extension</td>
<td>64 ± 10</td>
<td>66 ± 10</td>
<td>0.532</td>
</tr>
<tr>
<td>Supination</td>
<td>74 ± 13</td>
<td>77 ± 9</td>
<td>0.316</td>
</tr>
<tr>
<td>Pronation</td>
<td>66 ± 12</td>
<td>65 ± 12</td>
<td>0.937</td>
</tr>
<tr>
<td>Grip strength (kg)</td>
<td>13.6 ± 5.3</td>
<td>13.8 ± 5.4</td>
<td>0.885</td>
</tr>
</tbody>
</table>

*The values are given as the mean and standard deviation, except for the proportion with healing at six weeks.
suppression of bone turnover, bisphosphonates can increase mechanical strength during the early healing phase as a result of increased callus.

In the present study, there was no delay in the healing of distal radial fractures fixed by volar locking plate fixation. One possible explanation is that the healing mechanism of distal radial fractures treated with rigid volar locking plate fixation involves primary bone healing between fragments rather than bridging due to external callus formation, which is necessary for the healing of non-stabilized fractures such as those used in many animal models. Furthermore, there can be a difference between mainly cancellous and cortical bone fractures. In fractures of compact long bones, fracture bone debris must be absorbed to allow room for new-bone formation; thus, a resorption process is critical initially. However, distal radial fractures involve cancellous bone, in which the space for new-bone formation is larger than that in compact bones. Therefore, we speculate that the healing of distal radial fractures stabilized by a volar plate may not be suppressed by a reduction in the resorption process by bisphosphonates because of the spacious environment offered by cancellous bone.

When an osteoporotic radius is fractured, thin cortical walls are easily crushed, and impacted cancellous bones usually result in a metaphyseal defect, which may increase the initial radial deformity. Sakai et al. demonstrated a significant association between bone mineral density and radiographic radial deformity. However, Milliez et al. found no correlation between the degrees of comminution and displacement and the degree of osteoporosis. In the present study, fracture type was not correlated with bone mineral density and the time to radiographic union was not correlated with bone mineral density or fracture type. Although the presence of osteoporosis can compromise the maintenance of reduction achieved by cast application or pinning, it appears that healing is unaffected by the degree of osteoporosis or the bone defect type in patients in whom a distal radial fracture is fixed by a volar locking plate. Furthermore, in one study, the augmentation of metaphyseal defects with bone substitute material after volar locking plate fixation offered no benefit over volar locking plate fixation alone.

Several limitations of the present study should be mentioned. First, we defined radiographic fracture union as bridging by trabeculae or osseous bone across fracture lines, as previously described. However, the interobserver reliability of determination of fracture union was not high. Furthermore, there is a lack of consensus regarding the definition of fracture union in the current orthopaedic literature, which makes fracture care studies difficult to interpret. Newer methods, such as measuring callus size on computed tomography scans, may be necessary for a quantitative assessment of radiographic union. Second, the patients and treating physicians were not blinded because the medication was started at different times, and some of the measurements (wrist motion and grip strength) were done by the senior author, which is a source of bias. However, individuals who were unaware of the group allocations performed the radiographic assessments and administered the DASH questionnaires. Third, our patients had received the diagnosis of osteoporosis for the first time before being enrolled in the study, and they took only one type of bisphosphonate (alendronate). Thus, we are unable to comment on whether patients taking bisphosphonates for a long time before surgery and those taking other forms of bisphosphonate would have had similar results. Fourth, our sample size was calculated to determine a two-week difference in the time to radiographic healing between the groups. Thus, statistically, we can only assert that bisphosphonate treatment did not cause a fourteen-day difference in the time to radiographic union. Furthermore, the sample size was too small to detect clinically important complications such as nonunion.

Future investigation should focus on whether early bisphosphonate intervention actually increases the osteoporosis treatment rate for patients with an osteoporotic distal radial fracture treated with volar locking plate fixation did not affect fracture-healing or radiographic or clinical outcomes, although our sample size was too small to detect a rare complication of nonunion. Future investigation should focus on whether early bisphosphonate intervention actually increases the osteoporosis treatment rate for patients with a distal radial fracture.

Appendix
A table showing the demographic characteristics of the patients is available with the online version of this article as a data supplement at jbjs.org.
References


