

Timing of Bisphosphonate Initiation After Fracture: What Does the Data Really Say?

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Abstract

Introduction: Osteoporosis is often not clinically recognized until after a fracture occurs. Individuals who have 1 fracture are at increased risk of future fractures. Prompt initiation of osteoporosis treatment following fracture is critical to reducing the rate of future fractures. Antiresorptives are the most widely used class of medications for the prevention and treatment of osteoporosis. Many providers are hesitant to initiate antiresorptives in the acute post-fracture period. Concerns include interference with bone remodeling necessary for successful fracture healing, which would cause increased rates of non-union, malunion, and refracture. While such concerns should not extend to anabolic medications, physicians may also hesitate to initiate anabolic osteoporosis therapies due to high cost and/or lack of familiarity. This article aims to briefly review the available data and present a digestible narrative summary to familiarize practicing orthopaedic surgeons with the essential details of the published research on this topic. **Results:** The results of 20 clinical studies and key pre-clinical studies related to the effect of anti-resorptive medications for osteoporosis on fracture healing are summarized in the body of this narrative review. **Discussion & Conclusions:** While few level I studies have examined the impact of timing of initiation of osteoporosis medications in the acute post-fracture period, the few that have been published do not support these concerns. Specifically, data from level I clinical trials indicate that initiating bisphosphonates as early as 2 weeks post-fracture does not increase rates of non-union or malunion. By reviewing the available data, we hope to give clinicians the confidence to initiate osteoporosis treatment promptly post-fracture.

Keywords

osteoporosis, pharmacology, fragility fractures, trauma surgery, geriatric trauma, metabolic bone disorders

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Introduction

Osteoporotic fractures are estimated to affect 50% of women and 20% of men at some point in their lives.¹ Osteoporosis is considered a silent disease since it is commonly not identified until one or more osteoporotic fractures has occurred. Because of this, prompt initiation of screening and treatment for osteoporosis is increasingly being recognized as part of the orthopaedic surgeon's scope of practice in elderly patients presenting with fractures. Given this emerging responsibility, it is important to combat misconceptions that may serve as barriers to initiating care in this population. Perhaps the most common misconception regarding osteoporosis medications is that they cannot be initiated in the immediate post-fracture period without interfering with fracture healing. As this is often the first period in which osteoporosis is recognized and the only period when the patient has regular contact with the

orthopaedic surgeon, combating this misconception can help to promote prompt initiation of osteoporosis care by the orthopaedic surgeon or another professional in the orthopaedic department (e.g. a fracture liaison or bone health service). This article aims to briefly review the available data to rapidly familiarize practicing orthopaedic surgeons with the essential details of the published research on this topic. Because the vast

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Table 1. Brief Summary of Clinical Studies and Key Pre-Clinical Studies Related to the Effect of Anti-Resorptive Medications for Osteoporosis on Fracture Healing.

Study	Agent	Rx start	Design	N	Conclusion
Colon-Emeric et al ²	Zoledronic acid (Bisphosphonate)	After fracture	RCT (secondary outcome)	2127	Rx use, timing of rx use (0-2, 2-4, 4-6, 6+ weeks) post-fracture not associated with delayed fracture healing. Limited power in first 2 weeks
Kim et al ³	Risedronate (Bisphosphonate)	After fracture	RCT (primary outcome)	90	No difference in time to radiographic fracture healing between rx use at 1 week, 1 month, 3 months s/p internal fixation of intertrochanteric femur fracture
Gong et al ⁴	Bisphosphonate	After fracture	RCT (primary outcome)	50	No difference in time to radiographic union or clinical outcomes (DASH score, grip strength, wrist motion) between rx start 2 weeks vs 3 months s/p volar plate fixation for distal radius fracture
Seo et al ⁵	Bisphosphonate	After fracture	RCT (primary outcome)	82	No difference in time to radiographic union or clinical outcomes (Constant and ASES scores) between rx start 2 weeks vs 3 months s/p locking plate fixation for proximal humerus fracture
Rozental et al ⁶	Bisphosphonate	Before fracture	Retrospective cohort	196	Clinically insignificant delay in radiographic union (55 vs 49 days) of distal radius fracture
Ha et al ⁷	Bisphosphonate	Before fracture	Prospective cohort	105	Increased prevalence of IVC sign at 3 months relative to no Rx. No change in height loss, kyphosis, VAS score, ODI score at 3 months.
Solomon et al ⁸	Bisphosphonate	Before or after fracture	Retrospective Case-Control Analysis of Medicare Claims Data	19,731	Surgical intervention for non-union occurred more commonly in individuals who began a bisphosphonate after their proximal humerus fracture (RR = 2.37 95% CI 1.13-4.96) but not in individuals who were taking bisphosphonates before their fracture (RR = 0.84, 95% CI 0.19-3.74). Similar analyses for raloxifene and calcitonin were inconclusive
Amanat et al ⁹	Zoledronic acid (Bisphosphonate)	After fracture	Rat model, RCT	125	Rx administration at 1 or 2 weeks post fracture achieved greater callus strength than rx administration at time of fracture (44% and 50% greater strength than controls vs 30% greater strength than controls)
Gerstenfeld et al ¹⁰	Alendronate vs denosumab	After fracture	Mouse model, RCT	110	Both bisphosphonate and denosumab treated individuals had greater callus strength and delayed cartilage remodeling relative to controls
Cummings et al ¹¹	Denosumab	Before fracture	RCT (secondary outcome)	7,868	No evidence of higher delayed union rate. Limited by small number of delayed unions (2 in rx, 4 in placebo).

RCT = Randomized Controlled Trial. Rx = the pharmaceutical agent being studied. S/p = status post. DASH = Disabilities of the Arm, Shoulder, and Hand score. ASES score = American Shoulder and Elbow Surgeons score. VAS = visual analog scale for pain. ODI = Oswestry Disability Index. CI = Confidence Interval.

majority of prescriptions for osteoporosis are for bisphosphonates, the majority of this review is dedicated to that class. The key findings of the studies discussed in this review are summarized in Table 1.

Rationale for Delayed Initiation of Bisphosphonates Post-Fracture

Commonly used bisphosphonates work by attaching to the hydroxyapatite binding sites on bony surfaces, especially those undergoing active resorption. When osteoclasts resorb bone into which bisphosphonate has incorporated, the bisphosphonate is released and impairs osteoclast function in several

ways, including adherence to bone surface, formation of the ruffled border, and generation of the protons necessary for bone resorption. In nitrogen-containing bisphosphonates (including zoledronic acid, risedronate, alendronate, and others), this action is mediated by inhibition of farnesyl pyrophosphate synthase, part of the mevalonate pathway, the disruption of which inhibits protein prenylation, thereby interfering with the aforementioned osteoclast functions and decreasing bone resorption. Simple bisphosphonates (such as etidronate and tiludronate), in contrast, generate metabolites within osteoclasts that exchange with the terminal pyrophosphate of adenosine triphosphate (ATP), depriving osteoclasts of a necessary energy source and causing apoptosis. In both cases, diminished

osteoclast action produced decreased bone resorption. Because bone formation by osteoblasts is not similarly affected, these changes slow net loss of bone mass. Bone resorption plays an important role in normal bone remodeling by removing poor quality bone to make room for new bone deposition. Bone remodeling is thought to play an important role in fracture healing by allowing consolidation of the callus into a normal appearing bone. Many surgeons are therefore concerned that inhibiting bone resorption may interfere with normal fracture healing, possibly causing delayed union, non-union, or mal-union.^{2,3,5,12}

Clinical Data

Use After Fracture

Four level I clinical trials have examined the impact of initiation of bisphosphonates in the acute post-fracture period on fracture healing, including rates of non-union.

In a pre-specified subgroup analysis of the Health Outcomes and Reduced Incident with Zoledronic Acid Once Yearly (HORIZON) Recurrent Fracture Trial, delayed union occurred in 3% of the 2127 patients who were randomized to either placebo or zoledronic acid.² For reference, nonunion rates for displaced femoral neck fractures range from 10-30%, whereas non-displaced fractures have a <5% nonunion rate, and intertrochanteric fractures a <2% rate.⁴ No association was observed between zoledronic acid and delayed hip fracture healing (OR 1.17 95% CI 0.72-1.90, $p = 0.61$) and no observed temporal trend between timing of zoledronic acid initiation and delayed healing when comparing individuals started on either zoledronic acid or placebo within 2 weeks of fracture, between 2 and 4 weeks, between 4 and 6 weeks, and greater than 6 weeks post-fracture. Of note, less than 5% of the patients included in the study ($n = 102$, $N = 2127$) were started on either zoledronic acid or placebo within 2 weeks of fracture. Because so few patients were included in that group and only approximately 3% of patients in any group had delayed unions, limited statistical power was available to detect a difference between those started on zoledronic acid within 2 weeks and those started at other time periods. Therefore, the lack of a statistically significant difference between individuals started on zoledronic acid during the first 2 weeks and those started at later timepoints should be interpreted with caution. Notwithstanding this caveat, the data from the HORIZON trial provide one of the most potent tests of whether bisphosphonates inhibit bone healing because (1) zoledronic acid is the most potent bisphosphonate currently on the market, (2) it was given in a single IV dose large enough to last 1 year, (3) the HORIZON trial was the largest bisphosphonate RCT conducted to date, and (4) non-union events were prospectively evaluated by an independent data safety monitoring board. Those 4 factors should have helped to identify an effect of zoledronic acid on fracture healing had one existed. Overall, the results of this pre-planned secondary analysis of adjudicated non-union data from the HORIZON trial suggest timing of initiation of bisphosphonates

post-fracture does not impact the rate of hip fracture non-unions.

Kim et al found mean time to fracture healing did not differ significantly between individuals starting risedronate 1 week after surgery, 1 month after surgery, or 3 months after surgery ($p = 0.42$) in a multicenter prospective trial investigating the timing of bisphosphonate initiation following internal fixation of intertrochanteric femur fractures in 90 patients.³ Gong et al found no differences in clinical outcomes or radiographic parameters, including time to radiographic union, between individuals randomized to start bisphosphonates at 2 weeks vs 3 months post-fracture (6.7 vs 6.8 weeks, $p = 0.65$) in a randomized controlled trial of 50 osteoporotic women 50 years of age and older undergoing volar locking plate fixation for distal radius fracture.¹² Clinical outcomes were measured using wrist motion, grip strength and the Disabilities of the Arm, Shoulder and Hand (DASH) score. Seo et al found no delay in radiographic fracture union or clinical outcomes between those who started a bisphosphonate 2 weeks post fracture compared to those who began a bisphosphonate 3 months post-fracture in a level III retrospective review of 82 patients treated with locking plate fixation for proximal humerus fractures at a single institution.⁵ Clinical outcomes were measured using Constant and American Shoulder and Elbow Surgeons (ASES) scores.

These studies collectively suggest starting bisphosphonates 2 weeks or more after a fracture does not increase the rate of non-unions, mal-unions, or the time to radiographic union among patients who were not previously on a bisphosphonate. While the published clinical data suggest starting bisphosphonates in the first 2 weeks post fracture may be safe, the relatively paucity of data from this early time period makes us hesitant to recommend initiating bisphosphonates during the first 2 weeks post fracture.

Prior Bisphosphonate Use

Bisphosphonates are known to persist in the bone and remain pharmacologically active for years. A 1997 level II study found the half-life of a single IV dose of alendronate was more than 10 years in bone.¹³ A later level I study found that a single IV dose of zoledronic acid was still suppressing markers of bone turnover 5 years after administration.¹⁴ Bisphosphonates may take up to 3 months to reach maximum efficacy.^{15,16} The long persistence of bisphosphonates in bone and their relatively slow onset of action suggest that bisphosphonate use prior to fracture may impact fracture healing, even if use after fracture does not. To date, 2 clinical studies have examined the impact of prior bisphosphonate use on time to radiographic fracture union. In a retrospective review of 196 consecutive distal radius fracture patients, Rozentel et al found patients taking a bisphosphonate prior to a distal radius fracture took a statistically but not clinically significantly longer time to reach radiographic union than individuals who were not on a bisphosphonate prior to fracture (55 vs 49 days, $p = 0.03$).⁶ In a prospective study of 105 patients with osteoporotic spinal fractures who were managed conservatively, Ha et al found the

presence of an intravertebral cleft sign, indicating delayed fracture healing, was more common in patients with prior bisphosphonate use than those without (30% vs 20.5%, $p < 0.05$).⁷ Changes in height loss and kyphosis during the 3 months post fracture did not differ significantly between those taking bisphosphonates prior to fracture and those who were not. Oswestry Disability Index scores and pain ratings on the Visual Analog Scale did not differ significantly between the 2 groups at 3 months post fracture. Thus, Ha et al found an increased incidence of intravertebral cleft sign among individuals who were taking bisphosphonates prior to osteoporotic vertebral fracture relative to those without prior bisphosphonate therapy. They did not identify any additional height loss, changes in kyphotic angle, or differences in clinical outcomes on the Visual Analog Scale or Oswestry Disability Index between groups. These 2 studies together suggest bisphosphonate use prior to fracture may impede radiographic fracture healing but do not appear to impact clinical outcomes at 3 months post-fracture.

The clinical literature on bisphosphonates suggest bisphosphonate use prior to fracture may delay radiographic but not clinical healing, while use after fracture does not delay radiographic or clinical healing.

Insurance Claims Data

A level III retrospective review of Medicare insurance claims data found use of a bisphosphonate after proximal humerus fracture was associated with an increased rate of surgical interventions for non-union, while bisphosphonate use before fracture was not.⁸ These results directly conflict with the above reviewed results from clinical trials, which found use after fracture was not associated with delayed union while use prior to fracture was. It is unclear whether this discrepancy is related to the nature of the insurance claims data used, the fracture type investigated, the use of operative intervention for non-union as the clinical measure of delayed union, or another variable. In the absence of stronger evidence, we tend to trust the preponderance of direct level I, II, and III clinical studies over a single pharmacoepidemiologic study.

Biomechanical Data

A wide variety of animal biomechanical studies have been published examining the impact of bisphosphonates on fracture healing. Two narrative reviews by Larsson and Fazzalari and Kates and Ackert-Bicknell focused on the biomechanical data for bisphosphonate use in the post-fracture setting. Both concluded that bisphosphonates (1) promote stronger callus formation, (2) delay remodeling, and (3) do not delay fracture healing.^{17,18} One notable study deserves special mention: in a rat fracture model, Amanat et al found that callus strength was greater on post-mortem strength testing when bisphosphonates were initiated 1 to 2 weeks post fracture rather than during the first week.⁹ The findings from this literature that bisphosphonates delay fracture remodeling without impacting healing

time could help explain the clinical findings reviewed above that patients taking bisphosphonates before fracture may have delayed radiographic evidence of fracture healing without impact on clinical outcomes.

Other Antiresorptives

RANK-L Inhibitor (Denosumab)

The RANK Ligand inhibitor denosumab (Prolia) inhibits osteoclast precursors from differentiating into mature osteoclasts. This causes an antiresorptive effect. While less data has been published on denosumab than bisphosphonates, it appears to have similar effects on bone healing, with one study demonstrating increased callus formation, increased bone mineral density, and no delay in fracture healing in mice.¹⁰ The Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial examined the rate of delayed unions following fractures among individuals taking denosumab for primary fracture prevention and did not find an increase in delayed unions relative to placebo, but the small number of cases of delayed unions (2 in denosumab group, 4 in placebo) makes this result difficult to extrapolate.¹¹

Strontium Ranelate

Strontium ranelate has not been approved by the US FDA for use in osteoporosis but is in use in Europe and elsewhere. Its mechanism is not well understood. It is postulated to have a mixed mechanism of action including antiresorptive and anabolic mechanisms, but most available data suggest a predominantly antiresorptive mechanism.¹⁹⁻²¹ A 2007 study of tibia fracture healing in rats suggested strontium ranelate did not impact fracture healing in either direction.¹⁹ A 2016 study of fracture healing in rabbits treated with strontium ranelate raised concerns that it might interfere with the acute phase of fracture healing.²⁰ A 2016 level I study investigating the use of strontium ranelate as an adjuvant to accelerate fracture healing in wrist fractures did not demonstrate a benefit and did not assess for inhibition of fracture healing.²¹ Overall data on the impact of strontium ranelate on fracture healing are unclear and caution should be used in considering the use of this medication in the acute post-fracture period.

Conclusion

The preponderance of available data suggests that all FDA approved medications for osteoporosis are safe to initiate as early as 1-2 weeks into the acute post-fracture period. Bisphosphonates and denosumab, which share an antiresorptive mechanism of action, increase callus size and strength, decrease bone turnover, and do not affect fracture healing rate. Pre-clinical data from a single study suggest that starting bisphosphonates 1-2 weeks post fracture may produce greater callus strength than starting them within the first week. Insufficient clinical data is available to rigorously assess outcomes when bisphosphonates are initiated in the first week post

fracture. Data from the few available level I studies do not support concerns that initiating FDA-approved anti-osteoporosis pharmacotherapy in the acute post-fracture period will interfere with fracture healing. The conclusion we have drawn based on the best currently available evidence is that it is safe to start bisphosphonate therapy in the acute post fracture period. These findings may change as additional studies are reported.

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