**Harding AK, Dahl AW, Geijer M, and et al. A single bisphosphonate infusion does not accelerate fracture healing in high tibial osteotomies. Acta Orthopaedica 2011; 82(4):465–470.**

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**Design:** Randomized clinical trial

**Objective:** To determine whether a post-surgery single infusion of zoledronic acid reduces the time to clinical osteotomy healing compared to a control infusion.

**Population /sample size/setting:**

- A total of 46 participants (10 females, 36 males, mean age 49 years) who underwent a tibial osteotomy and were operated on for knee OA by the hemicallotasis technique (HCO) were included in the study. At 4 weeks postoperatively, the patients were randomized to the intervention group who received an intravenous infusion of zoledronic acid or to the control group who received intravenous sodium chloride.
- Study design was randomized, assessor and patient blinded, controlled trial.
- Inclusion criteria included age between 35 and 65 years and osteoarthritis or deformity of the knee requiring surgery.
- Exclusion criteria included kidney, liver, or odontological disorders; rheumatoid arthritis; or bisphosphonate treatment two years or less before surgery.

**Interventions/Methods:**

- Four weeks postoperatively, randomization was performed by one of the authors using closed envelopes. The patients received an infusion of either zoledronic acid (4 mg intravenously or sodium chloride (9 mg/mL) prepared by the unblinded nurse. The infusion of zoledronic acid was prepared by diluting 4 mg zoledronic acid in 100 mL sodium chloride (9 mg/mL) and the zoledronic acid or saline solution was given as a 15-min intravenous infusion.
- The osteotomy was performed in well-vascularized metaphyseal bone where the access to circulation and cells was high.
- The patients were blinded regarding the type of infusion.
- The primary outcome was clinical fracture healing, evaluated blind, to determine whether one single infusion of zoledronic acid could reduce the time to fracture healing.
- Secondary outcomes were pin fixation (another study), bone mineral density and content of the osteotomy gap, drug safety, function measured with the knee-specific KOOS questionnaire, and retention of surgical correction.
- Assessment measurements for healing were taken first at 8 weeks postoperatively, by obtaining radiographs of the lower leg without weight bearing. Radiographs and ultrasound examination were performed at 10 weeks and every second week to evaluate healing until there was radiographic and clinical healing. Healing was evaluated blind, with extraction of the external fixator as the endpoint.

- The KOOS questionnaire was filled in preoperatively, and at 8 and 10 weeks and every second week postoperatively, until extraction of the external fixation. It was also filled in at the 20-week and 1.5-year follow-up.
- The bone mineral density (BMD) and the bone mineral content (BMC) were measured on the lower leg and bilateral proximal femur at 10 weeks postoperatively. The total T-score of the proximal femur was used to determine whether the patients had osteoporosis (< –2.5 SD), osteopenia (–1 to –2.5 SD), or normal bone.
- Radiographs were taken at a mean of 20 months after surgery to evaluate the retention of the surgically achieved correction.
- All drug-related side effects, complications, and adverse events were registered during the study.
- A power analysis to define sample size was performed and determined that 25 samples would be needed in each group to achieve a power of 95% at $p = 0.05$ in a two-sided test, with an estimated mean difference of healing time of 20 days between the bisphosphonate group and the control group.

**Main outcome measures/Results:**

- At baseline, demographic characteristics did not differ between the groups.
- All osteotomies healed with no difference in healing time between the groups. The time in external fixation was the same in both groups: 77 (95% CI: 75–80) days in the zoledronic-treated group and 77 (CI: 74–81) days in the control group. The mean difference was 0.2 (CI: –4.4 to 4.8) days. Seventeen of 25 patients in the zoledronic group and 18 of 21 patients in the control group had healed after 10 weeks in external fixation.
- The KOOS score improved over time in both groups. No statistically significant difference was found between groups for both physical function and pain. There were only small, statistically nonsignificant differences observed between the groups.
- Bone mineral density and bone mineral content were similar between the groups. Bone mineral density of the healing tissue in the osteotomy gap was 1.14 (SD 0.27) g/cm² in the zoledronic treated group, as compared to 1.01 (SD 0.18) g/cm² in the control group displaying no significant difference. None of the patients had osteoporosis, but 3 patients in the zoledronic-treated group and 6 in the control group had osteopenia.
- Radiographically, both groups retained the acquired correction at the 1.5-year follow-up.
- No difference was found between the 2 groups regarding complications. However, 13 of 25 patients reported muscle pain and influenza- like symptoms in the zoledronic group as compared to 2 of 21 in the placebo group (RR = 5, CI: 1.3–20; $p = 0.004$).

**Authors' conclusions:**

- Our results demonstrated no difference in the effect of zoledronic acid on fracture healing. With the time from surgery to extraction the same in both groups, it appears that the intervention of a single infusion of zoledronic acid did not shorten the healing time and did not exhibit any differences between the groups.
- In both groups, the external fixator was extracted almost 2 weeks earlier than in previous studies. The early extraction did not cause a loss of correction in either group.

- No loss of the surgically achieved correction was found in either group 1.5 years after surgery, and the values measured were within measurement error.
- No difference was found in bone mineral density or content between the groups.
- No negative effects of the drug regarding bone healing were found.

**Comments:**

- The first evaluation of healing with radiographs was performed after 10 weeks, a time point close to the clinical healing time of the osteotomies in both groups. Perhaps an earlier time point for evaluation of the effect of the drug should have been used, but the time from administration of the drug to extraction would then have been less than 6 weeks, which at the time of design of the study was considered the minimum time for the drug to have an effect. It's also important to give zoledronic acid at the time of ongoing fracture healing, since at that time a larger proportion binds to the fracture site than if given earlier at the time of the osteotomy.
- Zoledronate was not approved for osteoporosis treatment at the time this trial started.
- No difference was found in bone mineral density or content between the groups, which may indicate that a single dose, although efficient in animals, might be insufficient in humans. Perhaps a higher dose would have shortened the healing time, but the risk of side effects and unwanted effects such as local toxic effects to the osteoblasts would be higher. It is possible that continuous administration of a weekly oral dose of a bisphosphonate might have been more effective, but it is also possible that there is simply no or a very limited effect of the drug in fracture healing.
- Adequate sample size was determined to be 25 patients per group at 95% power. The study fell slightly short of this, but if an 80% power calculation had been used instead, the study would be adequately powered to detect a significant difference in healing time between the 2 groups.
- The number of adverse events of reported muscle pain and influenza- like symptoms observed in the zoledronic acid group as compared to the control group was significant. The safety of this drug for this purpose needs further evaluation before continuing its use.
- The study did not measure the success of assessor blinding. This is important, since the primary outcome of determining fracture healing could be subjected to possible assessor bias. Since no difference in the primary outcome was found, assessor bias was unlikely to occur.

**Assessment*:***

- This adequate study provides some evidence that a post-surgery single infusion of zoledronic acid is not effective in reducing the time to clinical osteotomy healing compared to a control infusion.