Intravenous zoledronic acid reduced new clinical fractures and deaths in patients who had recent surgery for hip fracture

Lyles KW, Colon-Emeric CS, Magaziner JS, et al. **Zoledronic acid and clinical fractures and mortality after hip fracture.** N Engl J Med. 2007;357:1799-809.

Clinical impact ratings: Hospitalists ★★★★☆☆ Geriatrics ★★★★★★

QUESTION

In patients who have had recent surgery for hip fracture, does intravenous (IV) infusion of zoledronic acid (once yearly) reduce clinical fractures?

METHODS

Design: Randomized placebo-controlled trial (Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly [HORIZON] Recurrent Fracture Trial).
Allocation: Concealed.*
Blinding: Blinded (clinicians, patients, outcome assessors, {data collectors, data analysts}†, monitoring committee, and study sponsor).*
Follow-up period: Median 1.9 years.
Setting: {148}† clinical sites in 23 countries.
Patients: 2127 patients ≥ 50 years of age (mean age 74 y, 76% women) with both legs, who had surgery for hip fracture from minimal trauma (i.e., fall from standing or lower height) within the past 90 days, were ambulatory before the fracture, and were unable or unwilling to take oral bisphosphonate. Exclusion criteria were previous use of strontium or sodium fluoride, hypersensitivity to bisphosphate, creatinine clearance < 30 mL/min, corrected serum calcium level > 11 mg/dL (2.8 mmol/L) or < 8.0 mg/dL (2.0 mmol/L), cancer, other metabolic bone disease, pregnancy, and life expectancy < 6 months.
Intervention: IV infusion of zoledronic acid, 5 mg, within 90 days of surgery and once yearly thereafter (n = 1065) or placebo (n = 1062). All patients received vitamin D and calcium supplements.
Outcomes: New clinical fracture (except of the face, digits, and abnormal bone). Secondary outcomes included vertebral, nonvertebral, and hip fractures; death; and adverse events.
Patient follow-up: 99% (intention-to-treat analysis).

MAIN RESULTS

The zoledronic acid group had fewer new clinical fractures, vertebral and nonvertebral fractures, and deaths than did the placebo group (Table). Groups did not differ for hip fractures (Table). Compared with placebo, the zoledronic acid group had higher risk for myalgia (3.1% vs 0.9%, P < 0.001) and pyrexia (6.9% vs 0.9%, P < 0.001) ≤ 3 days after infusion.

CONCLUSION

Intravenous infusion of zoledronic acid reduced new clinical fractures and deaths in patients who had recent surgery for hip fracture.

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*See Glossary.
†Information provided by author.

Zoledronic acid vs placebo in patients who had recent surgery for hip fracture‡

Outcomes at median 1.9 y	Zoledronic acid	Placebo	RRR (95% CI)	NNT (CI)
Any new fracture	8.6%	14%	33% (15 to 48)	22 (15 to 48)
New vertebral fracture	1.7%	3.8%	46% (8 to 68)	58 (39 to 335)
New nonvertebral fracture	7.6%	11%	26% (2 to 44)	37 (22 to 495)
New hip fracture	2.0%	3.5%	30% (–19 to 59)	Not significant
Death	9.6%	13%	27% (7 to 42)	29 (18 to 115)

‡Abbreviations defined in Glossary. RRR, NNT, and CI calculated from control event rates and hazard ratios in article.

COMMENTARY

Recurrent hip fractures are an important cause of mortality in elderly patients (1). Interventions that reduce fractures are needed. The study by Lyles and colleagues found that an annual infusion of zoledronic acid within 90 days after repair of hip fracture reduced the rate of new fractures. This is the first report of an effective intervention for secondary prevention of osteoporotic fractures in older persons. Adverse events usually occurred around the time of infusion, and the incidence of serious adverse events (i.e., atrial fibrillation) was not higher in the treatment group. These findings suggest that infusion of zoledronic acid once a year is safe and effective for preventing new clinical fractures.

The reduction in mortality was an interesting finding, but there was no published evidence that this reduction was associated with fewer new fractures. In fact, although the reduction in fractures could have had an indirect effect on reducing mortality (1), the most common causes of mortality in osteoporotic fractures after surgical repair are infections and complications related to trauma (2).

Not surprisingly, this study found a high incidence of vitamin D deficiency, and as a result, standard supplementation was given to all participants. Considering the age and characteristics of the study population, one would expect a large proportion to require vitamin D supplementation for the duration of the study. Additionally, use of a loading dose of vitamin D, although not fully supported by the current evidence, is probably appropriate considering calcium requirements before receiving IV treatment with bisphosphonates.

The study by Lyles and colleagues provides new evidence supporting the use of annual IV infusion for prevention of new osteoporotic fractures in older adults. This intervention should be supplemented with vitamin D and calcium.

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References

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2. **Vestergaard P, Rejnmark L, Mosekilde L.** Has mortality after a hip fracture increased? J Am Geriatr Soc. 2007;55:1720-6.