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Review Article

A literature review and case series of accelerating fracture healing in postmenopausal osteoporotic working women

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ABSTRACT

Majority of fractures do not cause significant long-term morbidity and mortality. A 10% of these fractures result in impaired fracture healing, drastically affecting quality of life in affected patients. Satisfactory healing of these osteoporotic fractures are critically important to functional recovery, morbidity, and quality of life. Some therapies for osteoporosis may affect the processes associated with bone repair. For example, bisphosphonates in experimental models are associated with increased callus size and mineralization, reduced callus remodeling, and improved mechanical strength. Local and systemic bisphosphonate treatment may improve implant fixation. No negative impact on fracture healing has been observed, even after major surgery or when administered immediately after fracture. For the osteoanabolic agent teriparatide, case reports and a randomized trial have produced mixed results, but they are consistent with a positive impact of teriparatide on fracture healing. At this point, therefore, there is no evidence that osteoporosis therapies are detrimental to fracture healing with some promising experimental evidence for positive effects on healing, notably for those agents whose actions are primarily anabolic.

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1. Introduction

The pathophysiology of fracture healing is complex, occurring in four phases. The first phase involves inflammation and formation of a hematoma at the site of fracture due to disruption of the blood supply at the site of injury.¹ In the second phase, chondrogenesis begins and a soft callus forms, which is then mineralized.¹ The third phase marks the

beginning of osteoblast cells forming woven bone, resulting in formation of a hard callus and union of the fracture.² In the final phase of fracture healing, remodeling of bone occurs, resulting in the formation of lamellar bone, which is mechanically stronger bone.²

Although the majority of fractures do not cause significant long-term morbidity and mortality, approximately 10% of these fractures result in impaired fracture healing, drastically

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affecting quality of life in affected patients. The pathophysiology of impaired fracture healing is largely unknown, certain risk factors have been well reported. Mechanical causes, such as insufficient immobilization of the fracture, distraction of fracture fragments by fixation devices, or repeated manipulations of a fracture, may lead to delayed or impaired union. Nonmechanical risk factors, including patient comorbidities, have also been suggested to result in impaired fracture healing. Diabetes, smoking, osteoporosis, and estrogen deficiency have all been identified as possible risk factors for impaired fracture healing.³ In such patient populations, impaired fracture healing may result in significant morbidity and negatively impact quality of life.⁴ With established risk factors for impaired fracture healing identified, there comes a greater need for therapy that can accelerate fracture healing in patients at high risk for delayed union or nonunion fractures.

By increasing bone formation, teriparatide, an anabolic agent used in the treatment of postmenopausal osteoporosis, has shown promise in accelerating the rate of fracture healing.

Patients experienced successful bony union of the fracture after the use of teriparatide. These findings suggest that teriparatide may be useful in the clinical setting for the acceleration of fracture healing, especially in patients who are at risk for impaired fracture healing.

Impaired fracture healing can have devastating consequences in this patient population, and may increase the fracture-related morbidity and mortality.

2. Review of literature

Andreassen et al were the first to report accelerated healing of fractures with teriparatide. Their study involved administering teriparatide to rats with tibial fractures. The results demonstrated enhanced callus formation and mechanical strength of tibial fractures in rats treated with teriparatide.^{5,6} In 2006, Manabe et al used teriparatide for fracture healing in cynomolgus monkeys, because their bone remodeling systems are closest to those of humans.⁷ In the study by Manabe et al, the results suggested that by attenuating the degree of mineralization and shrinking the size of the callus, teriparatide may have accelerated the rate of fracture healing.⁷ Although prior case studies regarding the use of teriparatide for accelerated fracture healing in humans exist, the only randomized, double-blind study in humans testing the hypothesis of acceleration of fracture repair was done by Aspenberg et al in 2010. In this study, involving 102 postmenopausal women with fractures of the distal radius, it was concluded that there was a shortened time of fracture healing in a group of patients using 20 µg of teriparatide compared with placebo.⁸ Their results suggest that teriparatide may lead to acceleration of fracture healing in humans.⁸

3. Case series

We treated twenty cases of postmenopausal working women with fractures who had osteoporosis the risk factor for impaired fracture healing, and report the time to fracture

healing with the use of teriparatide. All the patients had bone mineral density below -2.5 . All of them had normal values of Serum PTH, Vitamin D, Calcium and Alkaline phosphatase. Three of the patients have been treated non operatively. One of them sustained four part fracture of proximal humerus (Fig. 1).

Teriparatide, a drug approved for the treatment of osteoporosis in postmenopausal women, has shown promise in the realm of fracture healing. In the initial stages of fracture healing, an increase in bone formation is required. By increasing bone formation through stimulation of osteoblasts, teriparatide may accelerate the natural healing process of fractures. This may be useful in treatment of patients who have impaired fracture healing, ultimately affecting quality of life.

All the patients were started on a daily dose of teriparatide, 50,000 IU of Vitamin D3 once weekly and 2000 mg of calcium citrate.

Four weeks into therapy with teriparatide, repeat imaging revealed evidence of bony callus and new bone formation, consistent with a healing fracture (Fig. 2). The patients were pain free at this time, and shortly thereafter resumed all prior activities.

4. Discussion

Teriparatide, a recombinant human parathyroid hormone analog (1–34), was approved in 2002 by the Food and Drug Administration for the treatment of osteoporosis in postmenopausal women who are at high risk for fractures.⁹ The only anabolic agent available for the treatment of osteoporosis, its mechanism of action is unique in comparison with other agents used currently. Chronic exposure to endogenous human parathyroid hormone leads to an increase in bone resorption via stimulation of osteoclasts, further exacerbating the condition of osteoporosis.¹⁰ Teriparatide, because of its ability to reach peak serum concentrations in 30 min and return to nondetectable serum levels in a few hours, has the paradoxical effect of stimulating new bone formation by favoring stimulation of osteoblasts over osteoclasts.¹⁰ In the

Fig. 1 – X-ray right shoulder showing four part fracture proximal humerus before starting teriparatide.

Fig. 2 – X-ray shoulder of the same patient with evidence of callus formation, four weeks after starting teriparatide.

natural process of fracture healing, a transient increase in bone formation at the site of fracture occurs. By increasing cortical thickness and bone formation on all bone surfaces, teriparatide may accelerate and augment this process of increased bone formation and fracture healing that happens naturally.¹

5. Conclusion

Our cases reported here suggest the possibility of accelerating fracture healing with the use of teriparatide. The cost of teriparatide is approximately 6000 rupees for a one-month supply. Taking cost into account, it may be best used to accelerate fracture healing in those patients at high risk for delayed union or nonunion of fractures, or in patients who require a return to baseline activity at a faster rate than is possible with the normal healing process. This includes postmenopausal women and also includes a large percentage of the workforce where jobs entail manual labor or constant walking throughout the day. For those who have occupations that involve walking throughout the day, repeated stress on the foot from walking could delay healing of the fracture. Patients with jobs entailing manual labor may suffer a greater loss of income than the cost of teriparatide for 1 month, due to inability to return to work until healing of the fracture has

occurred. In addition, many employers may not allow being away from work for months, and this could result in loss of employment for the patient.

In patients with jobs where the loss of income is greater than the cost of treatment with teriparatide, the drug may be useful in acceleration of fracture healing, allowing earlier return to work.

Conflicts of interest

All authors have none to declare.

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