Osteogenic Potential of Teriparatide Adjuvant Therapy in Surgical Treatment of Femoral Fracture

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Introduction: Some femoral fractures are known to have high risk of treatment failure. It is also difficult to treat femoral nonunion. Various adjuvant nonsurgical modalities have been tried, none is exclusively effective in treating fractures or nonunions. Teriparatide is a recombinant human parathyroid hormone and is approved for osteoporosis treatment due to its osteogenic effect through three proposed mechanisms on bone formation [1]. The first is increase of osteoblast differentiation. The second is decrease of osteoblast apoptosis. The last is reactivation of lining cells that cover the surface of quiescent bone. As a result, the number of osteoblast increases and bone formation occurs with use of teriparatide [2].

Previous studies revealed teriparatide is effective as a nonsurgical treatment of femoral nonunion or an adjuvant treatment of osteoporotic fracture [3, 4]. However, question remains whether teriparatide demonstrates osteogenetic potential and is effective as an adjuvant medication after surgery for non-osteoporotic fracture or nonunion.

The purpose of this pilot study is (1) to evaluate the results of adjuvant teriparatide use for femoral fractures including nonunions and (2) to disclose the safety issue in its usage.

Methods: One of authors have prescribed teriparatide after surgery for nonunion or fracture of femur assessed to have high risk of treat failure when patients agreed off label use of teriparatide for fracture healing. Patients were followed-up monthly during medication and as needed after medication. Two dimensional plain radiographic examinations were routinely done at every visit. We utilized computed tomography (CT) to evaluate lesion preoperatively or union progression postoperatively if necessary. Patients followed up at least one year after medication are included in this study. Twelve patients were identified. Patients’ age was 65 years (range, 41 - 79 years), and there were two male and ten female patients. Their diagnosis was nonunion in 6 patients and fracture in 6 (Table 1).

Medical records and radiographic images were reviewed. Medication started median 14 days (range, 4 - 80 days) after the surgery and continued average 11 weeks (range, 4 - 20 weeks) depending on the bone formation and adverse reaction. Patients injected 20 μg of teriparatide subcutaneously once a day by themselves.

Union was evaluated clinically and radiologically. No pain on fracture site is assessed as a clinical union [5]. Radiologically, two criteria were used. When callus appears on plain radiograph, we considered union begins and calculated fracture healing response dividing largest diameter of the callus by the bone diameter at the fracture site on the same radiograph.[6]. The cortical continuity of more than 3 cortices was considered as a radiologic union [7]. Duration from medication to callus formation, radiological union, and clinical union are calculated.
The Spearman’s rho test was used to analyze if time from operation to medication or duration of medication correlates with time to get union after medication. A p value of <0.05 was considered significant.

**Results:** Eleven of twelve fractures united both clinically and radiologically within a year after teriparatide use. Callus appeared average 8 weeks (range, 4 - 28 weeks) after medication showing average 1.45 (range, 1.2 - 1.9) of fracture healing response. Union completed radiologically and clinically average 37 weeks (range, 12 - 75 weeks) and 41 weeks (range, 22 - 75 weeks) after the medication, respectively. Neither the interval from operation to medication nor the duration of medication correlates with the time required for union.

It is possible to compare fractured bone to opposite side using postoperative CT images in four cases. At the level where callus formed most abundantly, bony area of fractured side is average 1.5 (range 1.3 - 1.7) times larger than opposite side.

For 6 fracture cases, callus formation occurred average 5 weeks (range, 4 - 7 weeks) after the medication. Radiologic and clinical union occurred average 34 weeks (range, 12 - 49 weeks) and 34 weeks (range, 22 - 49 weeks) after medication, respectively.

For 6 nonunion cases, excluding one case that failed to get union, callus appeared average 11 weeks (range, 4 - 28 weeks) after the medication in five cases. Radiographic and clinical union completed average 41 weeks (range, 18 - 75 weeks) and 49 weeks (range, 27 - 75 weeks) after the medication, respectively.

There is one nonunion case failed to get union after teriparatide use following fourth surgical treatment. Callus did not appear until 6 months after medication and fifth operation was done.

There were two patients who showed adverse reactions after medication. One complained temporary nausea and muscle cramp for 2 weeks and symptoms disappeared without recurrence. Teriparatide was used for ten more weeks in this case. The other patient complained itching and skin rash at injection site every time she injected for 4 weeks and symptoms disappeared after she stopped medication. Both patients got union.

**Discussion:** This is the first successful report of adjuvant teriparatide use for femoral fracture and nonunion after surgery regardless of patients’ age or osteoporosis. The union rate is 91.7% (11 of 12). Callus appeared abundantly average 8 weeks after medication. This finding is coincide with the information that teriparatide is known to affect the initial bone formation [2]. Teriparatide medication may be safe. There was no serious adverse reaction of medication other than itching, muscle cramp, or nausea.

**Significance:** Even appropriate surgical treatment is a mainstay of femoral fracture treatment, adjuvant teriparatide use could be considered in exclusive conditions because of its osteogenic potential.

| Table 1. Preoperative diagnosis of patients prescribed with teriparatide. |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Nonunion(Atypical) | Nonunion(Atypical) | Fractures(Atypical) | Fractures(Atypical) |
| 6 (3)                   | 6 (3)                   | 6 (5)                   | 6 (5)                   |
| Shaft                   | Subtrochanter            | Shaft                   | Subtrochanter            |
Figure 1. Nonunion of femoral shaft fracture treated using adjuvant teriparatide for 12 weeks. CT images taken 12 weeks after operation show both intramedullary and extramedullary abundant callus formation.

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