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Original Article

Initiation of Monthly Minodronate Therapy at an Early Stage After Hip Fracture

Tsuyoshi Ohishi,[,1] Tomotada Fujita,[1] Daisuke Suzuki,[1] Tatsuya Nishida,[1] Ryo Okabayashi,[1] Kazufumi Yamamoto,[2] Hiroki Ushirozako,[3] Tomohiro Banno,[4] and Yukihiro Matsuyama[4]*

[1]Department of Orthopaedic Surgery, Enshu Hospital, Hamamatsu, Shizuoka, Japan; [2]Department of Orthopaedic Surgery, Aoyama Hospital, Toyokawa, Japan; [3]Department of Orthopaedic Surgery, Iwata Municipal Hospital, Iwata, Shizuoka, Japan; and [4]Department of Orthopaedic Surgery, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka, Japan

Abstract

The incidence of second hip fractures occurring within a year of initial fractures is 20%–45%. The high incidence of second hip fractures in this period can be attributed to the rapid bone loss that occurs during this time. Restoring bone mass at an early stage after hip fractures is critical for preventing subsequent fractures. The aim of this study was to investigate the efficacy of monthly minodronate therapy (50 mg/4 wk) for preventing bone loss over a 9-mo period following hip fractures. Minodronate was administered monthly to 51 patients (44 females), beginning within 3 mo after hip fracture surgery. The mean (±standard deviation) age of the patients was 82.0 ± 0.9 yr. Demographics, mobility status, bone turnover makers, and bone mineral density (BMD) in the lumbar spine and proximal femur (including femoral neck and total hip BMD) were examined prior to and after 9 mo of treatment. Lumbar BMD was increased by 2.7% ± 4.4% ($p < 0.001$) compared to the baseline values. However, femoral neck and total hip BMD did not significantly change. Bone formation and resorption markers both decreased by approximately 70% during treatment. Monthly treatment with minodronate did not adversely affect the healing process on the fracture site or the patients' laboratory results. The patients who were independently mobile prior to injury exhibited greater recovery of BMD in the femoral neck during the 9-mo treatment period. Monthly minodronate therapy during the early stages after hip fractures has favorable effects on restoring overall lumbar BMD and contralateral femoral neck BMD in patients with independent mobility prior to fractures.

Key Words: Bisphosphonate; bone mineral density; hip fracture; minodronate; surgery.

Introduction

As the population in Japan continues to age, the incidence of hip fractures also increases *(1)*. The incidence of second contralateral hip fractures following first fractures was previously reported to be 5%–10% *(2–4)*. Specifically, 20%–45% of second contralateral hip fractures occur within a year of the first fractures *(2,3)*. The accelerated rapid bone loss that occurs within a year of the first hip fracture is a contributing factor to the high incidence of second hip fractures during this period. Therefore, interventions to prevent rapid bone loss should be implemented immediately after the first hip fracture. Unfortunately, the rate of treatment with antiosteoporotic drugs in patients after hip fractures remains low (5%–20%) *(5–7)* despite the fact that the patients are candidates for osteoporotic drug interventions according to the guidelines for osteoporosis treatment in Japan *(8)*.

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*Address correspondence to: Tsuyoshi Ohishi, MD, PhD, Department of Orthopaedic Surgery, Enshu Hospital, 1-1-1 Chuo, Naka-ku, Hamamatsu, Shizuoka 430-0929, Japan. E-mail: t-ohishi@ken.ja-shizuoka.or.jp

Minodronate was developed in Japan; it is a third-generation bisphosphonate that contains an amino group in the imidazole ring *(9)*. An in vivo study illustrated that the antiresorptive efficacy of minodronate was 10- to 100-fold higher than that of alendronate or etidronate *(10)*. Studies ranging from 1 to 3 yr in duration have shown that daily minodronate treatment (1 mg/d) increased lumbar bone mineral density (BMD) and hip BMD by 6% and 3%, respectively, in a year and prevented vertebral fractures among female patients with osteoporosis *(11–14)*. Minodronate can also be expected to restore BMD in patients after hip fractures and prevent second hip fractures. In Japan, a monthly 50-mg oral formulation of minodronate has been available since September 2011. The monthly dosing regimen of minodronate was noninferior to the daily dosing regimen in terms of changes to lumbar and proximal femur BMDs and safety profiles *(15)*. Compared with the daily dosing regimen, the monthly dosing regimen is expected to result in improved patient compliance (medication adherence) and persistence, especially in the elderly population with hip fractures, in which dropout rates are extremely high *(16,17)*.

The primary objective of the present study was to investigate the efficacy of monthly minodronate therapy for preventing bone loss during a 9-mo period after hip fractures. The secondary objective was to examine the factors that affect changes in BMD after hip fractures.

Materials and Methods

The present study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by the institutional review board of Enshu Hospital (Hamamatsu, Shizuoka, Japan). Prior to this study, informed consent was obtained from all patients or their relatives.

The inclusion criteria of the study were that the patients should have undergone surgery for hip fractures and started monthly minodronate treatment after surgery in Enshu Hospital between October 2013 and May 2014. All patients sustained hip fractures caused by simple falls from standing at heights or falling at lower levels. Minodronate (Astellas Pharma Inc., Tokyo, Japan) was administered orally at a dose of 50 mg once every 4 wk to the patients (on an empty stomach) 2–12 wk after surgery. Any other treatment for osteoporosis including calcium, vitamin D, or hormone replacement therapy was not permitted during the study. Prior to drug administration and after 9 mo of treatment, the following procedures were performed: collection of blood and spot urine samples between 9:00 and 11:00 AM, examination of BMD in the lumbar spine and hip region, and radiography of the thoracic and lumbar spine. Radiographs of the surgery site were examined at baseline and every 2–4 wk after surgery. The exclusion criteria for the study were as follows: (1) admission with pathological fractures, (2) a previous history of contralateral hip fractures, (3) fractures within the previous 2 yr, (4) alcohol abuse, (5) treatment with any antiosteoporotic drug including hormone replacement therapy, (6) inability to walk, (7) hip fractures caused by high-energy trauma, (8) use of hemodialysis, and (9) conservative treatment. Hemiarthroplasty was performed for displaced femoral neck fractures by using Profemur Z (Wright Medical Technology Inc., Arlington, TN, USA) or AHFIX (Japan Medical Material Inc., Osaka, Japan), and osteosynthesis was performed for nondisplaced femoral neck fractures by using three 6.5-mm cannulated cancellous screws (Biomet Inc., Warsaw, IN, USA) or the Hansson Twin Hook System (Stryker Trauma AG Inc., Selzach, Switzerland). For trochanteric or infratrochanteric fractures, osteosynthesis was performed by using MIJ nail (Century Medical Inc., Tokyo, Japan) or long γ-nail (Stryker Inc.). Full weight-bearing gait was allowed 1 or 2 d after surgery.

BMDs of the lumbar spine (L2–4 in anteroposterior projection), femoral neck, and total hip in the proximal femur on the contralateral side were measured via dual-energy X-ray absorptiometry by using a QDR Discovery scanner (Hologic, Inc., Bedford, MA). The precision rate of the integral calcium hydroxyapatite standard was less than 0.4%. The serum levels of intact N-terminal propeptide of type 1 procollagen (P1NP) were measured by using an enzyme-linked immunosorbent assay with an intra-assay coefficient of variation of 6.6%–7.7% (Orion Diagnostica, Espoo, Finland). The urinary levels of cross-linked N-telopeptides of type 1 collagen (NTX) were analyzed by enzyme-linked immunosorbent assay with an intra-assay coefficient of variation of 7% (Osteomark; Osteox International, Seattle, WA). The NTX concentration was normalized to that of urine creatinine. All immunoassays were performed by SRL Inc. (Tokyo, Japan). Routine laboratory examinations including kidney and liver functions were also performed. The estimated glomerular filtration rate (eGFR) was calculated with the modification of diet in renal disease formula as follows: $eGFR\ (mL/min/1.73\ m^2) = 186.3 \times creatinine^{-1.154} \times age^{-0.203} \times 0.742 \times 0.881$.

Data Collection

The demographic factors investigated in the present study were age, sex, body mass index, fracture type (femoral neck or trochanteric/infratrochanteric fracture), operative method (endoprosthesis or osteosynthesis), mobility, presence or absence of dementia, comorbidity, time from admission to surgery, time of first administration of the drug, preexisting vertebral fracture, and occurrence of new vertebral or nonvertebral fractures during the study period. Delayed or nonunion of the fracture site after osteosynthesis and radiolucent zones around the endoprosthesis after hemiarthroplasty were evaluated on radiographs 9 mo after the start of drug administration.

Mobility before the injury and after 9 mo of drug administration was classified according to the ambulatory ability reported by Yonezawa et al *(18)*. The term "independent" was defined as the ability of the patient to walk without any aid or with a single cane. The term "dependent" was defined as the need for the patient to use a