Does bone healing take longer in fractures treated with bisphosphonates?

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ABSTRACT

Objectives: Bisphosphonates have become the gold standard treatment for osteoporosis, since they reduce the incidence of fractures. Recently, several papers have described the occurrence of low-energy atypical femoral fractures associated with the use of bisphosphonates. The objective of this study was to compare the average time to healing of atypical femoral fractures in patients who received bisphosphonates and in a control group. **Materials and Methods:** We retrospectively evaluated 34 patients with atypical femoral fractures, 16 of whom had received treatment with bisphosphonates for at least 5 years, between 2006 and 2017, and whose fractures were stabilized with a cephalomedullary nail. They were compared with a control group of similar characteristics. **Results:** All patients were female, with an average age of 74 years. Twenty-two (22) fractures were subtrochanteric, while 12 involved the femoral shaft. Fourteen percent (14%) of the patients who received bisphosphonates and surgical management required a revision surgery, while only 5.5% of the control group did. The average time to bone healing was longer in those treated with bisphosphonates (8.5 months vs. 6 months), which was statistically significant (p <0.001). **Conclusions:** The benefits of using bisphosphonates for fracture prevention outweigh the risk of atypical fractures. However, it is important to evaluate the risk-benefit ratio in each patient at the beginning of the treatment and during the course of it, since, despite the benefits, healing time is longer.
Keywords: Bisphosphonates; atypical femoral fractures; osteoporosis.
Level of Evidence: IV

¿Tardan más en consolidar las fracturas asociadas a bifosfonatos?

RESUMEN

Introducción: Los bifosfonatos evolucionaron como el pilar para el tratamiento de la osteoporosis, reduciendo la incidencia de fracturas. Recientemente, varias publicaciones describieron la aparición de fracturas atípicas de fémur de baja energía asociadas con el uso de bifosfonatos. El objetivo de este estudio fue evaluar el tiempo promedio de consolidación de las fracturas atípicas de fémur asociadas al tratamiento con bifosfonatos comparado con el de un grupo de control. **Materiales y Métodos:** Se evaluó, en forma retrospectiva, a 34 mujeres (edad promedio 74 años) con fracturas atípicas; 16 de ellas habían recibido bifosfonatos, al menos, por cinco años. Fueron tratadas entre 2006 y 2017, y estabilizadas con un clavo cefalomedular. Este grupo fue comparado con un grupo de control de similares características. **Resultados:** Veintidós tenían fracturas subtrocantéricas y 12, diafisarias. El 14% de las que tomaron bifosfonatos y fueron operadas requirió una revisión frente al 5,5% del grupo de control. El tiempo promedio de consolidación fue mayor en las tratadas con bifosfonatos (8.5 vs. 6 meses), con una diferencia estadísticamente significativa (p <0,001). **Conclusiones:** El beneficio del tratamiento con bifosfonatos en la prevención de fracturas es superior al riesgo de fracturas atípicas; sin embargo, es importante evaluar la relación riesgo-beneficio en cada paciente al comienzo y durante el tratamiento, teniendo en cuenta que, pese a esto, el tiempo de curación es más largo.
Palabras clave: Bifosfonatos; fracturas atípicas de fémur; osteoporosis.
Nivel de Evidencia: IV

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INTRODUCTION

Bisphosphonates have become the gold standard treatment for osteoporosis by increasing bone mineral density and preventing fragility fractures in osteoporosis patients.[1-7] As a result of inhibition of bone resorption (through the inhibition of osteoblasts), bisphosphonates may cause remodeling suppression with microdamage or microfracture accumulation which, through the impairment of its repair, alter bone quality.[8-11] This may compromise the mechanical and regenerative properties of bone, resulting in fractures and delayed bone union.[8,10-14] Several studies have reported a higher risk of atypical femoral fractures in patients taking bisphosphonate medications (low-energy fractures).[15-17]

Several recent studies have addressed the surgical treatment, the complications and the union rates of atypical femoral fractures.[18,19] Although the precise prognosis is still unknown, there is a growing consensus that altered bone metabolism caused by long-term bisphosphonates therapy would negatively affect fracture union, even following internal fixation.[20-22] A major concern exists about failed or delayed union after fracture stabilization in patients taking bisphosphonates.[23]

It is key to determine which factors have a positive or negative impact concerning the healing of atypical femoral fractures.

The objective of this study was to compare the average time to healing of atypical femoral fractures in patients who received bisphosphonates and in a control group.

MATERIALS AND METHODS

Based on the operative data from four surgeons, we retrospectively identified patients that had been initially treated for femur fractures extending from the subtrochanteric region to the supracondylar region, from 2006 to 2017, that had been receiving a bisphosphonate therapy at the time of the atypical femoral fracture and had been doing so for at least five years, and that had either no trauma history or a history of minor trauma. We then compared them to a control group consisting of patients with similar age and of the same sex who had sustained fractures extending from the subtrochanteric region to the supracondylar region and were not on a bisphosphonate therapy at the time of the fracture. Minor trauma was defined as a fall while standing or from a standing height.[24] A doctor asked all patients whether they were on bisphosphonates or whether they had been taking them, and for how long they had been taking them.

We exclude patients who had high-energy injuries, cancer within the previous five years, and diseases associated with pathologic fractures (e. g., hyperparathyroidism, renal failure, osteodystrophy or osteomalacia).

We only included patients who had sustained fractures with at least one of the following features: 1) femur fracture associated with minimal or no trauma; 2) non-comminuted or minimally comminuted fracture; 3) fracture line that originates at the lateral cortex and is transverse in its orientation, although it may become oblique as it progresses across the femur; 4) complete fractures that extend through both cortices and may be associated with a medial spike, and incomplete fractures involve only the lateral cortex; and 5) localized periosteal or endosteal thickening of the lateral cortex that is present at the fracture site, according to the American Society for Bone and Mineral Research criteria.[25]

We retrospectively documented patient demographics (age, sex), comorbidities, and fracture and surgical characteristics (including injury mechanism, fracture site, and time period between fracture and surgery) of all the patients. All fractures were stabilized with a statically locked cephalomedullary nail as first-choice therapy

Fracture union was defined as bony bridging on anteroposterior and lateral radiographs. XX. Successful bone healing was defined as fracture unions that take place within 6 months from surgery; on the other hand, delayed healing was was defined as fracture unions that do not take place within that time period. Surgeon criteria to diagnose bone healing was: 1) full weight-bearing ability; 2) no pain in the fracture site; and 3) radiographic evidence of bone healing.

All tests were conducted using the Stata 14.0 program (Statacorp LP. College Station, TX, USA, 2015).

RESULTS

In our study, all 34 patients were female and 16 received bisphosphonates. Fifty percent (50%) had been taking bisphosphonates for more than five years. The average age was 74 years (standard deviation [SD] 12), 10% were <50 years old, and there were no significant differences between both groups ($p = 0.502$). Fourteen percent (14%) of the patients who received bisphosphonates and surgical management required revision surgery, while only 5.5% of the control group did ($p = 0.051$).

Twenty-two (22) fractures were subtrochanteric, while 12 involved the femoral shaft. Sixty-eight percent (68%) of the patients who received bisphosphonate therapy had a shaft fracture, and 88% who did not receive the therapy sustained a subtrochanteric fracture (p = 0.001). There was no significant difference concerning which femur was affected (right or left, p = 0.746).

Bone healing time was significantly associated with bisphosphonate therapy: it was approximately twice as fast in the control group as in the bisphosphonate group (regardless of treatment time). The average time to bone healing in the control group was 6 months (SD 1.5) (25th percentile = 4 months; 75th percentile = 10 months), while in the bisphosphonate group was 8.5 months (SD 1.7), and 10% of the bisphosphonate group patients required more than 10-year period to achieve bone healing (and only 5% less than 5 months). This difference was independent of intake period (below or above five years; p = 0.791), namely, the average time to bone healing in the group that had received bisphosphonates for less than five years was similar to that of the group that had received bisphosphonates for at least five years, and both groups had a significantly longer average healing time to the control group (p = 0.0049) (Figure 1).

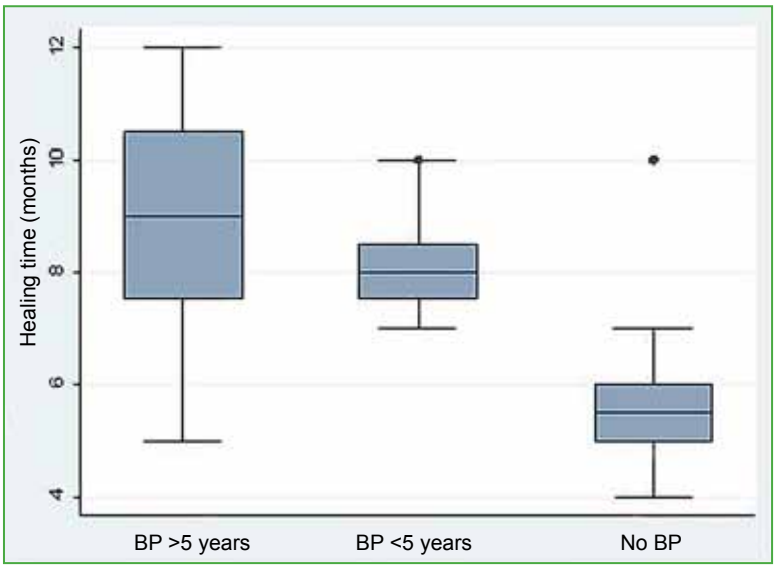

Figure 1. Box plot of the healing time (months) for the three groups of patients: with bisphosphonate intake >5 years; with bisphosphonate intake <5 years; without bisphosphonate intake (difference between bisphosphonate intake and no-bisphosphonate intake groups; p = 0.0049)

DISCUSSION

Bisphosphonates are the most commonly prescribed medications to treat diseases characterized by osteoclast-mediated bone resorption such as osteoporosis, Paget disease, or some tumor-associated, whether primary or metastatic, bone diseases.[27] The currently most widely used bisphosphonates are alendronate, ibandronate and zoledronic acid, and although they differ in potency, dosing schedules, and administration route, they have all proved effective for the prevention of fractures since they reduce the rate of bone resorption, increase bone density, and improve trabecular connectivity.[28,29]

The short-term benefits of these agents in osteoporosis patients have been shown, as they reduce the number of fractures in postmenopausal women; however, there are concerns regarding their long-term use. Over the past years, there have been reported cases of subtrochanteric stress fractures associated with these agents' long-term therapy; these fractures are typically transverse or slightly oblique, sometimes simultaneous bilateral fractures, and commonly result in displacement following low-energy trauma or even spontaneous fractures.[14,25,30-35]

Although its physiopathogenesis remains unknown, the transverse fracture pattern on the tension side of the femur, the presence of pain before the fracture is radiographically evident and lateral cortical hypertrophy suggest a stress fracture and that changes in bone remodeling will hardly allow for healing without proper treatment. The proximal region of the femur has significant biomechanical requirements, which may account the location of these fractures.[32]

Rio *et al*.[32] published two cases of displaced femoral fractures in patients with alendronate therapy history, both fractures were treated with a cephalomedullary nail and bone union was achieved in both cases. Weil *et al*.[19] in their study on surgically treated femur fractures associated with long-term bisphosphonate use reported 17 displaced fractures that were treated with an intramedullary nailing and a healing rate of 54%, with the remaining 46% of patients requiring revision surgery.

Our study was comprised of 34 fractures, 18 (52.9%) healed within six months after surgery, while the remaining 16 (47.1%), associated with bisphosphonate therapy, had delayed healing or did not heal. In a previous study that evaluated 41 atypical, low-energy femur fractures associated with >5 years of bisphosphonate use, 98% (40 out of 41) were radiographically healed at a mean of 8.3 months (range, 2–18 months).[20] XX. This mean healing time is longer than that of typical femur fractures, which heal at a mean of 3-6 months.

Kang *et al*.[22] and Thompson *et al*.[36] concluded that the long-term bisphosphonate use is significantly associated with a higher rate of difficult healing, a conclusion that corresponds with the results of other studies. In our study, we failed to find any difference in the bisphosphonate intake period between patients with a successful healing and patients with a difficult healing. All patients that were on bisphosphonate therapy had delayed healing, regardless of the intake period.

These fractures are likely to result in pseudarthrosis and thus in internal fixation failure. Therefore, these fractures have to be treated on two levels: physiopathological and biomechanical. On the physiopathological level, the first approach is considering the immediate termination of the antiresorptive in patients with complete and incomplete fractures or radiographs that may suggest insufficiency or stress fractures progressing from a bisphosphonate-related fracture.[37] This approach may reduce the chances of sustaining a contralateral fracture up to 53%.

On the biomechanical level, the approach has to secure an internal fixation that would allow for a good fragment contact and a fast recovery. However, some studies have shown that 46% of fractures treated with medullary nailing warranted revision surgery[19] and that cortical thickening resulting in marked canal narrowing can make medullary nailing impossible.[38]

Although currently there are no controlled studies evaluating surgical treatment for bisphosphonate-related fractures, a recent review study[39] suggests that the preferred method of treatment for atypical subtrochanteric and diaphyseal femoral fractures is endochondral fracture repair since bisphosphonates inhibit osteoclastic remodeling. Therefore, the recommended approach is an intramedullary reconstruction with full-length reamed nails that protects from a potential new shaft femoral fracture.[39] Sliding screw-plate device do no contribute to endochondral fracture repair and have a high failure rate, so we do not recommend them as an internal fixation device for these type of fractures.

In our study, cephalomedullary nails were used for all patients and only two of them underwent revision surgery: one of them was on bisphosphonate therapy and a fixed-angle plate implant was used (Figure 2) with a good outcome, and the other, with a subtrochanteric fracture and no bisphosphonate therapy, underwent revision surgery with partial hip arthroplasty.

There have been reported cases of fracture pseudarthrosis treated with sliding screw-plate as well as with cephalomedullary nails. Our experience shows that cephalomedullary nailing for subtrochanteric fractures with transverse or short oblique configuration is an approach that offers biomechanical advantages, preserving the fracture hematoma and also allowing for an early weight-bearing rehabilitation, according to tolerance.

Despite many surgeons favoring intramedullary nailing, there is currently no consensus on which treatment should be considered for there fractures.

Figure 2. Revision surgery of a fracture associated with ibandronate therapy, with a fixed-angle nail and healing.

The limitations of this study are: 1) the number of patients was limited as it is hard to find numerous patients with a relatively rare injury; 2) although we analyzed certain intraoperative factors, such as nail entry point, proper reduction, and rupture of the bone cortex (key bone healing factors), they were not considered when analyzing the outcomes.

CONCLUSIONS

The benefits of using bisphosphonates for fracture prevention outweigh the risk of atypical fractures. However, it is important to evaluate the risk-benefit ratio in each patient at the beginning of the treatment and during the course of it. Notwithstanding the low incidence of atypical subtrochanteric and shaft femoral fractures that can be extrapolated from the main bisphosphonate long-term follow-up studies, and the few clinical cases or reviews that have been published proving that there is a greater risk for patients on bisphosphonates to sustain these type of fractures, there is no doubt that their occurrence has provoked alarm among the professionals that devote themselves to this condition.

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