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Effects of tiludronate on healing of femoral fracture in dogs

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Abstract

The clinical and radiological effects of systemic administration of tiludronate (bisphosphonate compound), was investigated on the healing of experimentally induced femoral fractures in twelve adult experimental dogs which were divided randomly into two groups (six for each). After induction of femoral bone fracture and intramedullary fixation, the dogs (TG) were treated with tiludronic acid, at 2 mg/kg body weight, subcutaneously, twice weekly, for eight successive weeks. In the control group (CG) the fracture was fixed by Steinman intramedullary pin and was left to repair spontaneously without further medical treatment. All dogs were followed for two months by daily clinical and weekly radiological examination. The results revealed that, treatment with tiludronate played a role in the enhancement of fracture healing process by increasing the formation of callus at the fracture site. Fracture lines declined week 3, and completely disappeared in week 4 in the TG group. In the CG group the fracture lines declined in week 4, and disappeared in week 5. This effect was clearly reflected clinically by the earlier enhancement in the use of the fractured leg by the animals in the TG group, in comparison to the CG group.

Keywords: Bisphosphonates, Fracture, Healing, Dog.
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تأثير التلدرونيت على التئام كسور عظم الفخذ في الكلاب

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الخلاصة

تم إجراء مقارنة لمعرفة التغييرات السريرية والشعاعية الناتجة من العلاج بالحقن الجهازي بعقار التلدرونيت (من مركبات البزفوسفونيت) لغرض التحري على شَفَاء الكسور البسيطة في عمد عظم الفخذ المستحدثةِ بشكل تجريبي في إثنا عشرَ كلبِ بالغ والتي قُسّمتَ بشكل عشوائي إلى مجموعتين (ستّة لكُلّ منها)؛ مجموعة العلاج: بعد احداث الكسر في عمد عظمِ الفخذِ وتثبيتها بواسطة مسمار ستينمان داخل النخاع عولجتْ الكلاب بحمض التلدرونيك بجرعة ٢ ملغ/كغم، تحت الجلد، وبمعدل جرعتين إسبوعياً ولمدة ثمانية أسابيع ابتداءً من تاريخ إحداث الكسر وتثبيته. مجموعْة السيطرة: ثُبّتَ الكسر المستحدثّ بواسطة مسمار ستنمان داخل النخاع وتركت للُشفاء آنياً بدون معالجةِ طبيةِ اخرى. تمت متابعة مجموعتي السيطرة والعلاج سريرياً يوميا وشعاعياً إسبوعيا لمدة شهرينَ. كشفت المعالجة بالتلدرونيت دوراً في تحسين عملية التئام الكسر وذلك من الزيَادَة في الدشبذ في موقع الكسرَ. حيث، خفت خطوطَ الكسر في الإسبوع الثالثِ، وإختفتْ بالكامل في الإسبوع الرابع في مجموعةِ المعالجة. في مجموعة السيطرةِ خفت خطوط الكسرَ في الإسبوع الرابع، وإختفتْ في الإسبوع الخامس. هذا التأثير عُكِسَ بشكل واضح سريرياً بالتحسين السابق في إستعمالِ الساق المَكْسُور بالحيواناتِ في مجموعةِ المعالجة، بالمقارنة مع مجموعة السيطرة.

Introduction

The physiological mechanisms of fracture healing have been the topic of active investigation for many years. Unlike other tissues that heal through the generation of scar tissue, bone heals by regenerating new bone (1,2). Until recently, the main progress has been in the surgical procedures, which have allowed solid stabilization of the fractured segments. The attempts to develop drugs to stimulate bone formation have not been successful yet, although the discovery of bone-forming growth factors, such as the bone morphogenetic proteins (BMPs), transforming growth factors (TGFs), fibroblast growth factors (FGFs), and others, raises hope that soon we shall make use of their anabolic properties (3).

Fracture healing is divided into 3 phases: inflammatory, reparative, and remodeling. Following the initial inflammation, new bone is formed by intramembranous ossification as well as endochondral ossification; these processes are predominately mediated by osteoblasts (4,5). This phase is followed by an extended period of remodeling involving osteoclasts that resorb the new woven bone and osteoblasts that replace this matrix with lamellar bone (6). As with homeostatic remodeling, the important functional outcome of the remodeling phase of fracture healing is the restoration of mechanical strength and stability (4, 5). The process of bone and fracture repair consists of an anabolic (bone forming) response and a catabolic (bone resorbing) response. In the absence of an anabolic response, anti-catabolic treatment alone does not lead to union in a rat femoral critical defect model (7). Treatment with bisphosphonate (BP) may require anabolic conjunctive therapy to ensure enhanced successful repair (7, 8).

Investigators have addressed the positive or negative influence of bone resorption inhibitors on fracture healing. Rather, emphasis has been largely on the inhibition of fracture incidence. However, with the wide use of the BP, more recently, attention has focused on whether these drugs are, in fact, deleterious to fracture healing. Therefore, experiments in various animals are now available, which investigate BP effects on the healing of fractures (3).

Over the years, there have been concerns about whether or not BP interferes with the fracture healing. Because they suppress bone remodeling, one might expect that BP interfere with fracture repair. In a growing rat model using incadronate, it had been reported that BP treatment resulted in a larger fracture callus and delayed maturation of the fracture (9). Alendronate treatment also suppressed remodeling of the fracture callus in ovariectomized rats (10). These changes may be secondary to inhibition of bone resorption because bone formation and resorption are intimately linked. Conversely, there are reassuring reports on this topic that show fracture callus remodeling is not a problem in several animal models unless very high doses of BP are used (11,12). In contrast to these concerns, there are now several reports suggesting that BP may actually enhance fracture repair, probably by stabilizing the fracture callus (7). The important potential applications of BP in orthopedics, including protection against loosening of prostheses (13), better integration of biomaterials and implants (14), improved healing in distraction osteogenesis (15),

The aim of the study was to find out the effects of tiludronate (tiludronic acid) on fracture healing in dog's femur.

Materials and methods

Twelve young adult dogs from both sexes were included in this study. The Mean ± SE of their age and body weight were 8.4 ± 4.8 months, and 6.2 ± 2.0 kg, respectively. All the dogs were from local breed and were physically healthy. During the course of the experiment, the dogs kept and strictly supervised in the animal's housing of the Department of Veterinary Surgery and Theriogenology, College of Veterinary Medicine, University of Mosul. The right femora of all animals were experimentally fractured by wire saw in the mid-diaphysis and fixed with Stainman's intramedullary pins (2.5 to 5 mm diameter) using the routine aseptic surgical procedures (16). After surgery, the dogs were randomly and equally (i.e., 6 dogs for each group) divided into two groups; treatment (TG) and control (CG) groups. Animals of the treatment group received tiludronic acid 2 mg/kg, subcutaneously, two times per week for eight successive weeks till sacrificed (Tildren ®; Tiludronic acid 50mg. By: CEVA SANTE ANIMAL, 33500 Libourne, Frankrijik). While, the control group did not received treatment with the bisphosphonate drug.

Plain X-rays of all fractured femora was taken at weekly schedule throughout the study course to all dogs.

Results

Clinical findings

The experimental dogs in either groups, shows similar clinical signs during the first three post-operative (P.O.) days. These signs were; loss of function to the operated fractured thighs, in addition to local inflammatory signs such as heat, swelling, tenderness, and painful to touch.

In the tiludronate treated group (TG), the local inflammatory signs were gradually disappeared toward the 4th and 5th P.O. days, and were completely dismissed at the 6th to 7th P.O. days. The animals at the early days of the 2nd P.O. week were mildly using their operated legs by lightly putting weight on the foot. From the 3rd P.O. week, the functional usage for the operated legs was progressively enhancing and the animals were using them normally at the 4th P.O. week. A moderate diarrhea and mild cough was

observed on the animals of this group, but none of the dogs died.

In the control group, the animals showed a relatively longer time to regain the functional leg usage on the operated limbs. The first trials by the dogs to put light weight on their operated leg were during the last days of the 2nd P.O. weeks up to the 3rd P.O. week. While, better functional leg usage was seen during the 4th P.O. week, but normal usage was observed at the 5th P.O. week.

Radiological findings

In treatment group (TG); the fracture line was obvious at the first P.O. week (Wk) with mild periosteal reaction, and toward the end of the 2nd P.O. week, a slight increase in the periosteal reaction of the external callus was found but the fracture line was still evident. While at the 3rd P.O. Wk, the increase in the periosteal reaction was obviously larger and the fracture line was starting to decline (Fig. 1) and being faint at the 4th P.O. Wk and completely disappeared at the 5th P.O. Wk (Fig. 3), but the periosteal reaction and the external callus formation was continuous. At the 6th and 7th P.O. Wks, X-ray features characteristically showed decline in the size of the external callus and cessation of periosteal reaction (Fig. 5). While remodeling phase for the fractured bones was usually starting by a continuous decline in the size of the external callus and reforming of their normal shape (Fig. 7).

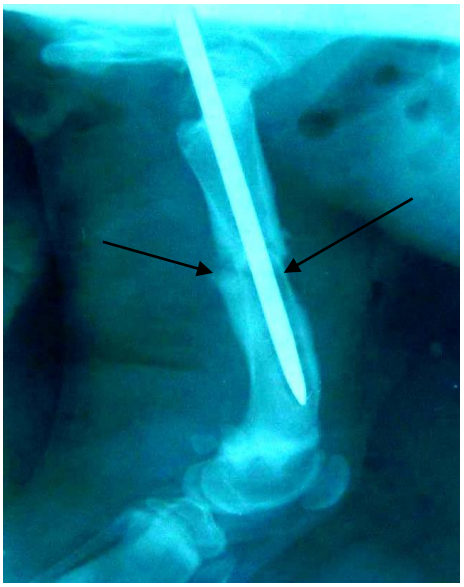

Fig. 1: TG, 3rd P.O. Wk., lateral view. Fracture line starting to decline with presence of periosteal reaction.

In the control group (CG); at the end of the 1st and 2nd P.O. Wks, the X-rays showed similar fetchers to those found in the treated group at the similar times. During the 3rd P.O. Wk, periosteal reaction was progressively dense and the fracture line was still very clear (Fig. 2). It was at the 4th P.O. Wk, when periosteal reaction was getting denser leading to disappearance of the fracture line which looks to be very faint at the 5th P.O. Wk (Fig. 4). At the 6th P.O. Wk, the fracture line was completely disappeared and at the 8th P.O. Wk the callus was largely declined in size and the bone started to reform itself (Figs. 8).

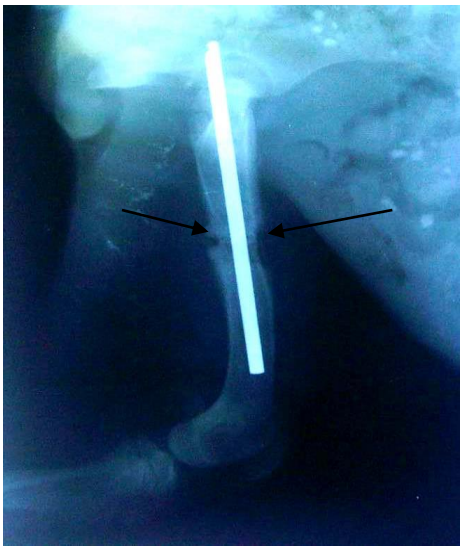

Fig. 2: CG, 3rd P.O. Wk., lateral view. Fracture line still clear with presence of periosteal reaction.

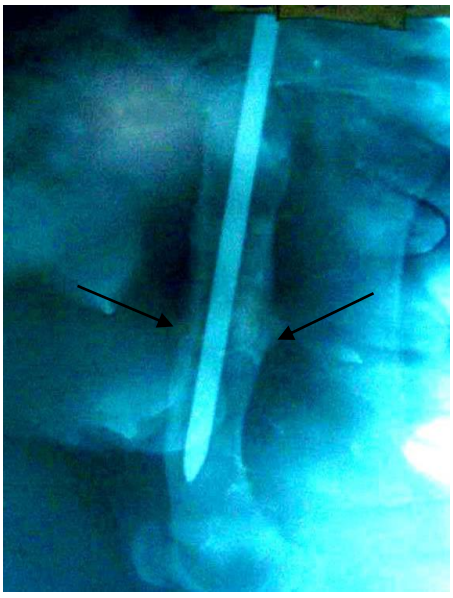

Fig. 3: TG, 5th P.O. Wk., lateral view. Fracture line disappeared, but periosteal reaction and callus formation continued

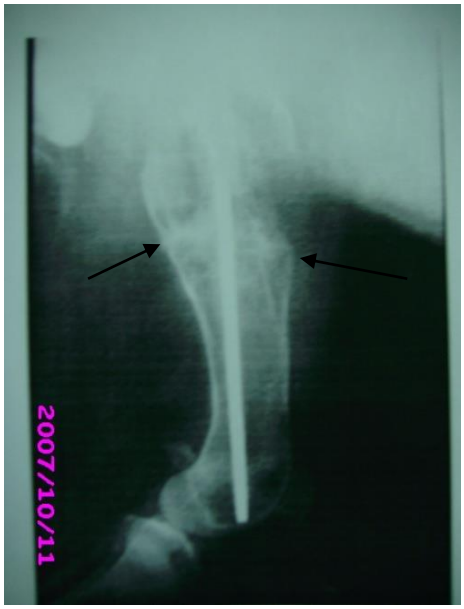

Fig. 4: CG, 5th P.O. Wk., lateral view. Fracture line almost disappeared, and periosteal reaction declined.

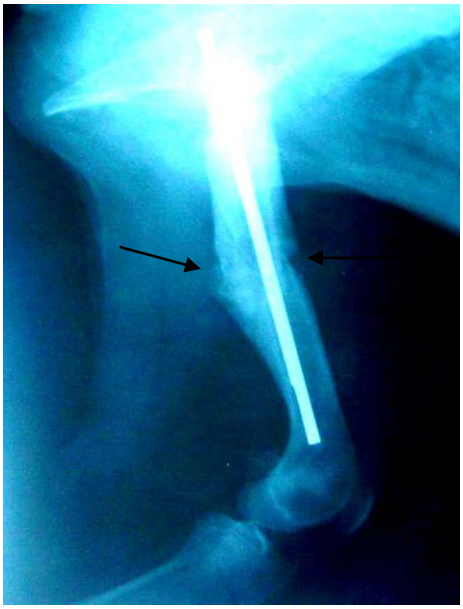

Fig. 6: CG, 6th P.O. Wk., lateral view. Complete disappearance of fracture line.

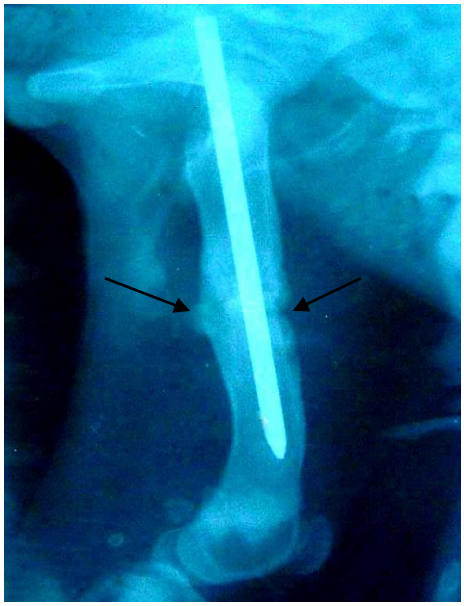

Fig. 5: TG, 6th P.O. Wk., lateral view. Decline in external callus and cessation of periosteal reaction.

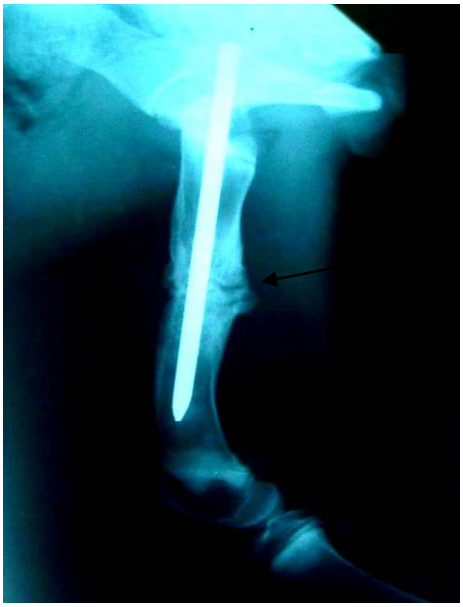

Fig. 7: TG, 8th P.O. Wk., lateral view. Bone started to reform its shape, and external callus continued to decline in size.

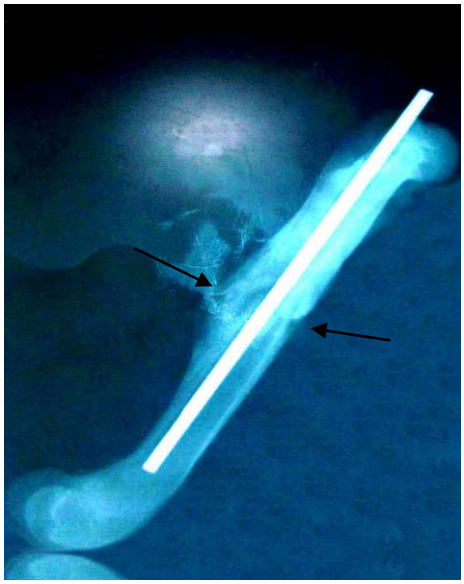

Fig. 8: CG, 8th P.O. Wk., lateral view. Bone reforming its normal shape, and the callus largely diminished in size.

Discussion

In the present investigation, tiludronic acid was found to enhance healing of the fractured femora of the dogs. This was noticed clinically and confirmed radiographically.

Clinically, the normally occurring post fracture pain was less assigned in the BP treated dogs. Loss of pain considered as one of the benefits in the usage of the BP for treatment of fractures (17), as well as in a wide variety of underlying bone conditions, such as osteolytic metastasis, multiple myeloma, and localized transient osteoporosis, (18,19). This relief of bone pain is mediated not only through the inhibition of osteoclast function, but also through an inhibition of cytokine production by macrophages and prostaglandin synthesis by a variety of cells (20). The earlier restore of the functional usage of the fractured leg by the BP treated dogs, which enabled them to lightly using their repaired legs from the end of the 1st P.O. week. While, in the non-BP treated dogs, restoration of the functional usage delayed for up to the 7 to 10 days, and was restored at about the last days of the 2nd P.O. weeks up to the 3rd P.O. week. This effect could mainly been specified due to the enhancement in the formation of callus which firmly support the fractured ends of the bone (Figs. 1 and 3). Several reports support this finding, suggesting that bisphosphonates may actually enhance fracture repair, probably by stabilizing the fracture callus (7). Also the used BP drug could improve osseointegration of the intramedullary metal implants in our tiludronate treated dogs (21).

Reports about whether or not bisphosphenates interfere with the fracture healing by suppressing bone remodeling (9), was not a problem in several animal models unless very high doses of bisphosphonates are used (11,12). The process of bone and fracture repair consists of an anabolic (bone forming) response and a catabolic (bone resorbing) response. In the absence of an anabolic response, anti-catabolic treatment alone does not lead to union in a rat femoral critical defect model (7). Bisphosphonate treatment may require anabolic conjunctive therapy to ensure enhanced successful repair (7, 8).

Although there have been concerns about bisphosphonates interfere with the fracture healing, because they suppress bone remodeling, one might expect that bisphosphonates interfere with fracture repair (9). The delay in the bone remodeling (Fig. 7) in the present study, did not interfered with the course of fractured bone healing process, because we did not used long courses of high doses of tiludronate treatment (11,12).

In conclusion, femoral fracture showed a good response to tiludronic acid treatment. The clinical course and radiological findings demonstrated the value of using this bisphosphenate drug for promotion of fracture healing.

Acknowledgement

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