Healing of bone fractures is a complex process that involves an inflammatory phase, restoration phase, and remodeling phase. In these processes, several growth factors and cytokines are produced and released at the fracture site. These local factors stimulate the recruitment, proliferation, and differentiation of mesenchymal stem cells into chondrocytes and osteoblasts; they also promote osteoblast proliferation for intramembranous ossification and chondrocyte differentiation into a soft callus for endochondral ossification. Healing is complete when mature lamellar bone is formed after woven bone has bridged the bone gap.1–3

One class of factors that mediates events in fracture healing is the PGs. They enhance bone resorption by increasing the number and activity of osteoclasts and stimulate bone formation by increasing the proliferation and development of osteoblasts.4 Prostaglandins also support maintenance of the blood supply to the fracture site through vasodilatation and vascularization via promotion of angiogenesis.5,6 Among the PGs, PGE_{2} is the most abundant PG in bone and has strong activity.7 Investigators in several studies5–12 have reported that the systemic and local injection of PGE_{2} or a PGE_{2}-receptor agonist stimulated bone repair in various animals.

Prostaglandins are derived from arachidonic acid via the action of 2 COX enzymes (COX-1 and COX-2). Cyclooxygenase-1 is expressed constitutively in several tissues (including bone) and is responsible for the production of PGs involved in homeostatic processes such as gastric cytoprotection, maintenance of renal homeostasis, and platelet functions.13–16 In contrast, COX-2 is typically expressed in only a few cell types, but its

Effects of long-term administration of carprofen on healing of a tibial osteotomy in dogs

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Objective—To evaluate effects of long-term administration of carprofen on healing of a tibial osteotomy in dogs.

Animals—12 healthy female Beagles.

Procedures—A mid-diaphyseal transverse osteotomy (stabilized with an intramedullary pin) of the right tibia was performed in each dog. The carprofen group (n = 6 dogs) received carprofen (2.2 mg/kg, PO, q 12 h) for 120 days; the control group (6) received no treatment. Bone healing and change in callus area were assessed radiographically over time. Dogs were euthanized 120 days after surgery, and tibiae were evaluated biomechanically and histologically.

Results—The osteotomy line was not evident in the control group on radiographs obtained 120 days after surgery. In contrast, the osteotomy line was still evident in the carprofen group. Callus area was significantly less in the carprofen group, compared with the area in the control group, at 20, 30, and 60 days after surgery. At 120 days after surgery, stiffness, elastic modulus, and flexural rigidity in the carprofen group were significantly lower than corresponding values in the control group. Furthermore, histologic evaluation revealed that the cartilage area within the callus in the carprofen group was significantly greater than that in the control group.

Conclusions and Clinical Relevance—Long-term administration of carprofen appeared to inhibit bone healing in dogs that underwent tibial osteotomy. We recommend caution for carprofen administration when treating fractures that have delays in healing associated with a reduction in osteogenesis as well as fractures associated with diseases that predispose animals to delays of osseous repair. (Am J Vet Res 2011;72:634–641)

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Abstract

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expression can be induced by a number of inflammatory cytokines. The end products of the upregulation of COX-2 activity are prostanoids, which contribute to pain and edema associated with inflammation.\textsuperscript{13-16} Additionally, mechanical loading and bone morphogenetic protein 2, parathyroid hormone, fibroblast growth factor 2, and transforming growth factor-β, all of which are related to bone metabolism, can induce COX-2 expression.\textsuperscript{13,16}

The NSAIDs are commonly used as postsurgical and posttraumatic analgesics. The primary action of NSAIDs is the inhibition of COX activity, which leads to a reduction in production of PGs. However, NSAIDs have several adverse effects (eg, gastrointestinal tract ulcers, decrease of platelet function, and renal damage) and these effects are associated with the inhibition of homeostatic (COX-1-mediated) prostanoids. Therefore, use of COX-2–selective NSAIDs, which inhibit COX-2 activity more than they inhibit COX-1 activity, may minimize these adverse effects.\textsuperscript{17,18}

In rodents, considerable evidence indicates that conventional nonspecific NSAIDs (eg, ibuprofen, ketorolac, and indomethacin) have an inhibitory effect on fracture healing.\textsuperscript{10-22} In studies\textsuperscript{23-27} conducted to compare nonselective NSAIDs and COX-2–selective NSAIDs in rats, impaired fracture healing was observed, with a greater effect seen in association with COX-2–selective NSAIDs. Moreover, in studies\textsuperscript{26-28} of COX-gene null mice, fracture healing was significantly delayed in the COX-2–null mice, compared with that in COX-1–null mice and mice with the wild-type genome. These results suggest that COX-2 activity is more important for fracture healing than is COX-1 activity.\textsuperscript{26,28}

In veterinary medicine, COX-2–selective NSAIDs are commonly used as analgesics after orthopedic surgery.\textsuperscript{29} It has been reported\textsuperscript{30} that the incidence rate for nonunion after fracture is 3.4% in dogs. There is a particularly high incidence of radial and ulnar nonunion in toy and miniature breeds, compared with the incidence in medium-sized dogs.\textsuperscript{31,32} Considering the results of these aforementioned studies, the use of NSAIDs as analgesics in dogs may inhibit the fracture healing process and contribute to delayed union or nonunion. However, we are not aware of any evidence in the veterinary medical literature concerning the effect of NSAIDs on fracture healing.

The objective of the study reported here was to compare healing after tibial osteotomy in dogs that were treated with carprofen or were not treated. The hypothesis was that healing after tibial osteotomy in dogs treated with carprofen would be impaired, compared with that in dogs receiving no treatment, as determined on the basis of radiologic, histologic, and biomechanical analyses.

**Materials and Methods**

**Animals**—Twelve healthy female Beagles were included in the study. All dogs were between 11 and 12 months of age at the beginning of the experiment. Surgical treatment and postoperative management of the dogs were performed in accordance with the Guidelines for Care and Use of Laboratory Animals of Nippon Veterinary and Life Science University. All experiments and animal breeding were performed at Nippon Veterinary and Life Science University.

**Treatment groups**—Dogs were allocated to 2 groups (carprofen group and control group; n = 6 dogs/group). Allocation was performed in 2 steps. In the first step, the smallest diameter of the bone marrow cavity was measured on mediolateral radiographs and dogs were ranked in descending order on the basis of diameter. In the second step, dogs were placed into blocks of 2; dogs in each block were assigned via a randomization procedure to the 2 groups. Dogs assigned to the carprofen group received carprofen\textsuperscript{2} (2.2 mg/kg, PO, q 12 h) for 120 days; administration of carprofen was initiated on the morning of the tibial osteotomy. Dogs in the control group received no treatment.

**Tibial osteotomy**—Tibial osteotomy was conducted as described in other studies.\textsuperscript{33,34} Each dog received preanesthetic injections of droperidol (0.25 mg/kg, IM) and buprenorphine (0.02 mg/kg, IM). Anesthesia was induced with propofol (7 mg/kg, IV); each dog was intratracheally intubated, and anesthesia was maintained with isoflurane and oxygen. Each anesthetized dog received epidural injections of buprenorphine (5 µg/kg) and bupivacaine (1 mg/kg). The right hind limb was aseptically prepared, and an incision was made to expose the craniomedial aspect of the diaphysis of the right tibia. Transverse osteotomy in the middle of the tibial diaphysis was accomplished by use of an oscillating bone saw\textsuperscript{3} with copious amounts of saline (0.9% NaCl solution). The full length of the bone marrow cavity was internally fixed with an intramedullary pin,\textsuperscript{3} and the wound was closed via routine procedures. To prevent rotational instability, an acrylic bandage\textsuperscript{4} was applied to the limb for 4 weeks after surgery. Postoperative analgesic management was achieved by administration of buprenorphine (0.02 mg/kg, IV, q 12 h for the first 3 days after the osteotomy, then 0.02 mg/kg, IM, q 12 h for the subsequent 11 days). If the investigators believed that a dog needed additional medications to control pain, additional doses of buprenorphine (0.02 mg/kg, IM) were administrated. However, none of the dogs received > 3 buprenorphine injections/d. Each dog received ampicillin sodium (25 mg/kg, PO, q 12 h) for 14 days after the osteotomy. Movement and weight loading of the right limb were allowed without limitation after the osteotomy.

**Radiographic analysis**—Mediolateral and craniocaudal radiographic projections were obtained immediately after the osteotomy (day 0) and at days 20, 30, 60, 90, and 120. In accordance with a method reported in another study,\textsuperscript{35} the area of periosteal callus was measured at each cortex (medial, lateral, cranial, and caudal) over a 30-mm length proximal and distal to the original osteotomy site by use of image analysis software.\textsuperscript{5} The total area was calculated as the sum of the areas of the callus for the 4 cortices.

**Euthanasia and CT analysis**—Each dog was euthanized via administration of an overdose of sodium pentobarbital at 120 days after osteotomy. Both tibiae were excised. The intramedullary pin was removed from the right tibia, and CT\textsuperscript{6} was performed for both
tibiae of each dog. The tibiae then were placed in phosphate-buffered 10% formalin until subsequent analyses were performed.

Biomechanical analysis—For the biomechanical analysis, a 3-point bending test was performed in accordance with a method reported by our laboratory group33,34 by use of a universal testing machine.5 The crosshead speed and distance between the supporting points on the shaft of the tibia were 5 mm/min and 60 mm, respectively. From the load-displacement curve, the structural mechanical properties were determined as maximum load to failure and stiffness. The load-displacement data were normalized to obtain intrinsic material properties, such as maximal stress, elastic modulus, and flexural rigidity. To measure the transverse area of a tibia, CT was performed on the region of the fracture line in all samples. On the basis of the CT images, the diameter of the bone and diameter of the bone marrow cavity were measured and the intrinsic material properties were calculated by use of the following equation35: maximal stress = (0.125 × maximum load to failure × the distance between the supporting points on the shaft of the tibia) / (diameter of the bone × area moment of inertia), where area moment of inertia = (π × [ (diameter of the bone)^4 ] – diameter of the bone marrow cavity)^4 / 64. Elastic modulus was calculated as stiffness × (distance between the supporting points on the shaft of the tibia)^3 / (48 × area moment of inertia). Flexural rigidity was calculated as the elastic modulus / area moment of inertia. To standardize the measured values among dogs, all variables for the right tibia were calculated as the recovery rate, which represents the ratio with regard to the left tibia (ie, [value of right tibia × 100] / value of left tibia).

Histologic examination—After the biomechanical analysis was completed, all samples were decalcified by incubation in 10% formic sodium citrate buffer for approximately 30 days at 25° to 30°C. After samples were embedded in paraffin, they were sagittally sectioned at a thickness of 5 μm. One median sagittal section was stained with H&E, and the adjacent 20 sections were alternately stained with safranine O–fast green and toluidine blue. The cartilage-to-cartilage area ratio was calculated as ([total cartilage area × 100] / total cartilage area) / (0.125 × maximum load to failure × the distance between the supporting points on the shaft of the tibia / diameter of the bone / area moment of inertia). Stiffness was calculated as (area × displacement) / load, and maximum load to failure was calculated as the maximal load and displacement at the point of failure. Elastic modulus was calculated as the slope of the load-displacement curve. For statistical analyses, the mean ± SEM of the values from all samples were determined. Differences in mean between the control and carprofen groups were tested by use of a 2-way ANOVA, and significance within each group was examined by use of the Tukey-Kramer test. Statistical analyses were performed with statistical software.34 Differences were considered significant at values of P < 0.05.

Results

Animals—At the initiation of the study, there were no significant differences (Student t tests) between the 2 groups for any of the variables. Mean ± SEM age of dogs in the control and carprofen groups was 11.8 ± 0.2 months and 11.8 ± 0.2 months, respectively. Mean body weight was 9.4 ± 0.5 kg and 10.5 ± 0.5 kg for the control and carprofen groups, respectively. Mean body condition score was 3.0 ± 0.3 and 2.8 ± 0.2 for the control and carprofen groups, respectively. Mean diameter of the medullary cavity at its narrowest point in the right tibia in the control and carprofen groups was 5.0 ± 0.1 mm and 5.2 ± 0.1 mm, respectively. Mean ratio of the intramedullary pin to the diameter of the medullary cavity at its narrowest point in the right tibia was 60.1 ± 1.4% and 58.7 ± 1.6% for the control and carprofen groups, respectively.

Radiographic analysis—In the control group, the osteotomy line had disappeared and sufficient callus had formed, as determined via examination of radiographs obtained 120 days after the osteotomy. In contrast, the osteotomy line had not entirely disappeared in radiographs obtained for the carprofen group on day 120 (Figure 2). The callus area was significantly increased in both groups at all time points after osteotomy, compared with preoperative values, except for the value at 120 days after osteotomy in the control group. The mean ± SEM callus area was significantly less in the carprofen group than in the control group at
20 (12.5 ± 2.5 mm² and 49.9 ± 9.4 mm², respectively \( [P = 0.004] \)), 30 (44.4 ± 12.3 mm² and 135.0 ± 29.1 mm², respectively \( [P = 0.010] \)), and 60 (142.0 ± 30.9 mm² and 292.8 ± 57.2 mm², respectively \( [P = 0.016] \)) days after osteotomy. In addition, the callus area in the control group was significantly \( (P = 0.002) \) less at 120 days than at 60 days after osteotomy (Figure 3).

**CT analysis**—As determined by evaluation of CT images at 120 days after osteotomy, the mean ± SEM transverse area of the osteotomy line in the right tibia was significantly \( (P = 0.040) \) greater for the carprofen group \( (174.7 ± 17.5 \text{ mm}^2) \) than for the control group \( (116.8 ± 17.3 \text{ mm}^2) \). However, the mean transverse area of the left tibia at 120 days after osteotomy did not differ significantly \( (P = 0.162) \) between the carprofen group \( (59.0 ± 1.8 \text{ mm}^2) \) and the control group \( (55.3 ± 1.6 \text{ mm}^2) \). Also, mean recovery rate at 120 days after osteotomy did not differ significantly \( (P = 0.065) \) between the carprofen group \( (52.9 ± 1.8\%) \) and the control group \( (58.1 ± 2.1\%) \).

**Biomechanical analysis**—The tibiae on which the osteotomy was performed failed through the fracture line at maximum load. Results of the biomechanical analysis were summarized (Table 1). Stiffness, elastic modulus, and flexural rigidity were significantly lower in the carprofen group than in the control group. Mean ± SEM stiffness for the carprofen and control groups was 306.3 ± 54.8 N/mm and 461.2 ± 41.2 N/ mm, respectively; these values differed significantly \( (P = 0.047) \). Mean elastic modulus differed significantly \( (P = 0.038) \) between the carprofen group \( (642.9 ± 270.0 \text{ MPa}) \) and the control group \( (1,645.7 ± 322.0 \text{ MPa}) \). Mean flexural rigidity differed significantly \( (P = 0.047) \) between the carprofen and control groups \( (1.4 ± 0.2 10^5 \text{ N/mm and 2.1 ± 0.2} 10^5 \text{ N/mm, respectively}) \). Additionally, recovery rate for stiffness, elastic modulus, and flexural rigidity were also significantly lower in the carprofen group than in the control group. Mean recovery rate for stiffness for the carprofen and control groups was 47.1 ± 7.7\% and 79.7 ± 6.6\%, respectively \( (P = 0.009) \). Mean recovery rate for elastic modulus for the carprofen and control groups was 11.0 ± 4.4\% and 28.5 ± 6.3\%, respectively \( (P = 0.046) \). Mean recovery rate for flexural rigidity for the carprofen and control groups was 47.1 ± 7.7\% and 79.7 ± 6.6\%, respectively \( (P = 0.009) \). Although not significantly different, other mechanical variables and their recovery rates typically were lower for the carprofen group than for the control group. There were no significant differences between the 2 groups.

![Figure 3](image-url)  
**Figure 3**—Mean ± SEM total callus area after osteotomy of the right tibia for 6 dogs treated with carprofen for 120 days (white circles) or 6 control dogs that received no treatment (black circles). Day of osteotomy was designated as day 0. *Within a time point, values differ significantly \( (P < 0.05; \text{Mann-Whitney U test}) \) between treatment groups. †,‡Within the control group, value differs significantly \( (P < 0.05; \text{± P = 0.001}) \) from the value for day 0. †,‡Within the carprofen group, value differs significantly \( (P < 0.05; \text{± P = 0.01; Tukey-Kramer test}) \) from the value for day 0. Table 1—Mean ± SE values for biomechanical analysis of samples obtained at 120 days after osteotomy of the right tibia in dogs in the control and carprofen groups \( * \) (n = 6 dogs/group).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tibia</th>
<th>Control</th>
<th>Carprofen</th>
<th>P value†</th>
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<tr>
<td><strong>Structural properties</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Maximum load (N)</td>
<td>Right</td>
<td>535.9 ± 50.8</td>
<td>542.6 ± 27.9</td>
<td>0.909</td>
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<tr>
<td></td>
<td>Left</td>
<td>929.4 ± 68.6</td>
<td>1,036.2 ± 68.9</td>
<td>0.301</td>
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<tr>
<td>Recovery rate (%)</td>
<td>Right</td>
<td>58.5 ± 6.3</td>
<td>53.5 ± 4.5</td>
<td>0.532</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>461.2 ± 41.2</td>
<td>396.3 ± 54.8</td>
<td>0.047</td>
</tr>
<tr>
<td>Recovery rate (%)†</td>
<td></td>
<td>79.7 ± 6.6</td>
<td>47.1 ± 7.7</td>
<td>0.009</td>
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<tr>
<td><strong>Intrinsic material properties</strong></td>
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<td></td>
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<tr>
<td>Maximum stress (MPa)</td>
<td>Right</td>
<td>41.1 ± 8.8</td>
<td>24.0 ± 3.6</td>
<td>0.102</td>
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<td>Left</td>
<td>159.3 ± 8.1</td>
<td>155.5 ± 5.9</td>
<td>0.713</td>
</tr>
<tr>
<td>Recovery rate (%)</td>
<td>Right</td>
<td>26.9 ± 6.8</td>
<td>15.6 ± 2.6</td>
<td>0.152</td>
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<tr>
<td></td>
<td>Left</td>
<td>6,143.0 ± 435.9</td>
<td>642.9 ± 270.0</td>
<td>0.038</td>
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<tr>
<td>Recovery rate (%)†</td>
<td></td>
<td>45.6 ± 0.3</td>
<td>11.0 ± 4.4</td>
<td>0.046</td>
</tr>
<tr>
<td>Flexural rigidity (10³ N/mm²)</td>
<td>Right</td>
<td>2.1 ± 0.2</td>
<td>1.4 ± 0.2</td>
<td>0.047</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>2.7 ± 0.3</td>
<td>3.0 ± 0.2</td>
<td>0.425</td>
</tr>
<tr>
<td>Recovery rate (%)†</td>
<td></td>
<td>79.7 ± 6.6</td>
<td>47.1 ± 7.7</td>
<td>0.009</td>
</tr>
</tbody>
</table>

* Dogs in the carprofen group received carprofen (2.2 mg/kg, PO, q 12 h) for 120 days after osteotomy, whereas dogs in the control group received no treatment. †Represents results of a Student t-test; means differ significantly between groups at values of \( P < 0.05 \). †Recovery rate is the ratio between the measured value for the surgically treated right tibia and the measured value for the intact left tibia. — = Not applicable.
for any of the mechanical variables in the contralateral (intact) left tibia.

**Histologic examination**—Mean ± SEM total callus area did not differ significantly ($P = 0.265$) between the control (65.9 ± 5.3 µm$^2$) and carprofen (58.3 ± 2.5 µm$^2$) groups. Mean cartilage area was significantly ($P < 0.001$) less in the control group (0.5 ± 0.1 µm$^2$) than in the carprofen group (2.8 ± 0.4 µm$^2$). Similarly, the mean cartilage-to-callus ratio was significantly ($P < 0.001$) lower in the control group (0.8 ± 0.1) than in the carprofen group (4.2 ± 0.5; [Figure 4](#fig4)). At higher magnification, hypertrophic condrocytes were observed in the nonmineralized cartilage; hypertrophic condrocytes were rarely detected in the nonmineralized cartilage of the control group ([Figure 5](#fig5)).

**Discussion**

Although NSAIDs have been used as postoperative analgesics in veterinary medicine, to our knowledge, there have been no reports on the effect of NSAIDs during fracture healing in dogs. In the study reported here, carprofen was used as a COX-2–selective NSAID and the inhibitory effect of carprofen on the healing process after tibial osteotomy in dogs was evaluated. The inhibitory effect of the carprofen group was characterized by a smaller callus size during the early stages of the osteotomy healing process, a delay in healing of the osteotomy, and greater cartilage content in the callus, compared with results for the control group, which led to a significant decrease in intrinsic material properties of the osteotomized tibiae. These observations are consistent with findings from other studies in rodents with experimentally induced fractures and indicate that long-term administration of carprofen inhibits fracture healing in dogs. Moreover, carprofen was administered at recommended therapeutic doses. Therefore, the administration of carprofen at recommended therapeutic doses may significantly inhibit the osteotomy healing process.

Intramedullary fixation with a Steinmann pin was used to stabilize the midtibial transverse osteotomy. In the present study, osteotomy healing was radiographically confirmed to proceed to a secondary union in all dogs. The mean anticipated healing times for typical uncomplicated fractures treated by various methods have been reported. Taking into consideration the ages of the dogs and the method of fixation used in the study reported here, the radiographic findings at 120 days after osteotomy indicated that bone union was completed within the anticipated time frame in the control group. Specifically, the osteotomy line had disappeared and sufficient callus had formed, as detected on the radiographs obtained at 120 days. At 90 and 120 days after surgery, the callus area was significantly less than at 60 days after surgery. These findings may also suggest the progression of external callus remodeling. In contrast, the osteotomy line did not completely disappear in the carprofen group. Although the callus development was also confirmed in the carprofen group, it was significantly reduced on sequential radiographs from 20 to 60 days after osteotomy, compared with that in the control group. Additionally, the transverse area of the osteotomy line at 120 days after osteotomy in the carprofen group was significantly larger than that in the control group. This result suggested that callus remodeling was delayed. Callus formation is one of the characteristics of secondary bone union. The findings of the present study indicated that carprofen inhibited callus formation during early stages of the healing process after tibial osteotomy in dogs. Because callus formation is related to intramembranous and endochondral ossification, our results may suggest that carprofen inhibits intramembranous and endochondral ossification.

In the histologic analysis, the cartilage area was significantly larger in the carprofen group than in the control group. Intramembranous and endochondral ossification.
were observed at higher magnification in the nonmineralized cartilage in the carprofen group but were rarely detected in the control group. These results are consistent with those in other studies that were conducted to evaluate the effect of several NSAIDs, such as diclofenac, ketorolac, valdecoxib, indomethacin, and rofecoxib, on fracture healing in rodents. Carprofen can significantly reduce the growth of osteophytes in dogs with experimentally induced osteoarthritis. Osteophyte formation is a common osteoarthritis feature, as is cartilage degradation, and it is recognized that osteophytes form through the endochondral ossification process. Thus, analysis of the findings in those other studies suggests that carprofen may inhibit endo-

Figure 5—Photomicrographs at low (A) and high (B) magnification of selected tissue sections obtained from dogs treated with carprofen for 120 days after a tibial osteotomy (top row in each panel) or dogs that received no treatment (bottom row in each panel). Tissue sections were stained with H&E (left column in each panel), Saf-O–fast green (middle column in each panel), or toluidine blue (right column in each panel). Notice the callus (C), cartilage tissue (asterisk), and hypertrophic chondrocytes (arrowheads). Bar = 500 and 50 µm for panels A and B, respectively.
chondral ossification in animals with osteoarthritis. In the present study, we observed obvious remains of cartilage tissue in the callus at 120 days after osteotomy in the carprofen group. This result may suggest that carprofen also inhibits endochondral ossification during the osteotomy healing process.

In the study reported here, the persistence of cartilage tissue in the callus of the carprofen group was also considered to be attributable to a decrease in callus formation. In the present study, the carprofen group had a small callus size. Callus formation is an important process to provide stability of a fracture site in secondary bone union.\(^{45}\) It is clinically recognized that instability of the fracture gap leads to delayed union or nonunion.\(^{42,43}\) Thus, the smaller amount of callus development in the carprofen group may have resulted in instability of the osteotomy gap, and this instability may have led to delayed union and cartilage remnants.

We did not detect significant differences between the 2 groups for any of the mechanical variables of the contralateral (left) tibia. Moreover, the mechanical variables for the intact left tibia in the present study were similar to those reported elsewhere.\(^{33,34,44,45}\) This result suggests that long-term administration of carprofen did not alter the mechanical features of an intact tibia in mature Beagles. On the other hand, the biomechanical variables and the recovery rate of osteotomized bone in the carprofen group were significantly lower at 120 days after surgery, compared with those in the control group. From a biomechanical viewpoint, strength of the bone increases with increases in transverse area and bone mineral density. Although the transverse area of the bone at the osteotomy site was larger in the carprofen group than in the control group, the intrinsic material properties were significantly less at 120 days in the carprofen group than in the control group. Considering the histologic results in the present study, the remaining cartilage in the callus may lead to decreases in bone mineral density. Thus, it may have been a reason for the decrease of bone strength in the dogs treated with carprofen.

A limitation of the present study was the fixation system used. Our laboratory group commonly uses intramedullary fixation with a Steinmann pin to stabilize a midtibial transverse osteotomy. We have investigated radiographic, histologic, and mechanical effects of this fixation on canine tibiae. In the control group of the present study, the radiographic and histologic findings and mechanical variables of the osteotomized tibiae were similar to those in other studies\(^{11,34}\) conducted by our laboratory group. Thus, we believe that the results observed for the tibial osteotomy performed in the present study are reproducible and highly reliable. However, this fixation system should not be used alone in clinical situations because this method does not provide rotational stability for transverse fractures or osteotomies. To the authors’ knowledge, there have been no reports of the evaluation of the effects of NSAIDs on fracture healing with a rigid fixation system, such as internal plate fixation. Moreover, in another study\(^{46}\) in which investigators compared mRNA gene expression during fracture healing between rats treated with an intramedullary pin and rats treated with internal plate fixation, it was reported that the expression pattern of genes related to inflammation, cell division, formation of cartilage, and macrophage activity was altered by the method of fixation. Thus, whether the use of another form of more rigid fixation would have altered the results of the present study is unknown.

The present study had another limitation. The osteotomy technique used in this study was not as traumatic as a fracture in clinically affected animals, and the degree of inflammation associated with fractures may not be attenuated to the same degree as with an osteotomy. Additionally, carprofen administration was begun before osteotomy in the present study; however, in most clinical situations, carprofen would not be started until after the fracture occurred. Although we do not believe that these differences would have dramatically altered the results of the present study, it should be emphasized that the conditions of the study reported here may not entirely reflect clinical conditions.

We concluded that the long-term administration of carprofen (2.2 mg/kg, PO, q 12 h) may inhibit healing of a tibial osteotomy in dogs. Carprofen-treated dogs had a small callus size during the early stages of the osteotomy healing process, a delayed union of the fracture, obvious cartilage contents in the callus, and significantly lower values for the intrinsic material properties of the healing tibiae. We believe that the results of this study may be applicable to fracture healing in animals in clinical situations. Although a prospective and blinded clinical study in dogs is needed to evaluate whether fracture healing is inhibited with carprofen administration in clinical situations, we recommend caution in carprofen administration when treating fractures with delayed healing associated with a reduction in osteogenesis as well as fractures in animals with diseases (eg, diabetes mellitus and hyperadrenocorticism) that predispose to delayed osseous repair.


