# Comparison of the analgesic efficacy of perioperative firocoxib and tramadol administration in dogs undergoing tibial plateau leveling osteotomy

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# Comparison of the analgesic efficacy of perioperative firocoxib and tramadol administration in dogs undergoing tibial plateau leveling osteotomy

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**Objective**—To evaluate the effect of perioperative oral administration of tramadol, firocoxib, and a tramadol-firocoxib combination on signs of pain and limb function after tibial plateau leveling osteotomy in dogs.

**Design**—Randomized, masked, prospective clinical trial.

**Animals**—30 adult client-owned dogs with unilateral cranial cruciate ligament disease.

**Procedures**—30 dogs were allocated into 3 treatment groups (tramadol, firocoxib, and a tramadol-firocoxib combination). Signs of pain (short-form Glasgow composite measure pain scale), serum cortisol concentrations, and limb function (pressure platform gait analysis) were recorded at several time points before surgery and through 3 days after surgery. Outcome measures were compared among groups.

**Results**—A significantly greater number of dogs in the tramadol group (8/10 dogs) had a pain score > 6 after surgery, compared with the other groups. No significant differences were detected in the pain scores between the firocoxib and the tramadol-firocoxib combination groups. There were no significant differences in serum cortisol concentrations among the 3 groups. Limb function was significantly decreased for dogs in the tramadol group on days 1 and 2 after surgery and in the firocoxib group on day 1 after surgery. Although limb function decreased for dogs in the tramadol-firocoxib combination group, the change was not significant for any day after surgery.

**Conclusions and Clinical Relevance**—Dogs that received firocoxib orally, alone or in combination with tramadol, had lower pain scores, lower rescue opiate administration, and greater limb function than dogs that received only tramadol. When used alone, oral administration of tramadol may not provide sufficient analgesic efficacy to treat dogs with pain after orthopedic surgical procedures. (*J Am Vet Med Assoc* 2013;243:xxx–xxx)

Stifle joint surgery induces moderate to severe pain in addition to inflammation in the joint. Goals of effective perioperative pain management in orthopedic surgery include accurate assessment of signs of pain and treatment with multimodal analgesia.

Firocoxib is a COX-1–sparing NSAID oral tablet that is FDA approved for the control of perioperative signs of pain and inflammation associated with orthopedic surgery in dogs. It is also approved for the control of signs of pain and inflammation associated with osteoarthritis in dogs. Oral administration of tramadol is commonly used in dogs for signs of pain, but it is not FDA approved. Orally administered tramadol is rapidly and unpredictably metabolized in dogs and has limited scientific evidence supporting its use as an effective perioperative analgesic.[1] However, tramadol is a central analgesic with a low affinity for μ-opioid receptors and may have some serotonin enhancement effects as well.[2] Given that these drugs have different mechanisms of action, it is possible that any analgesia provided by tramadol may complement that provided by firocoxib.

**Abbreviations**

| | |
|---|---|
| COX | Cyclooxygenase |
| GCPS | Glasgow composite measure pain scale |
| TPLO | Tibial plateau leveling osteotomy |

However, to the authors' knowledge, no previous studies have compared the safety or efficacy of tramadol and firocoxib in dogs.

Pain assessment in veterinary patients continues to be a challenge when assessment tools are typically subjective and external factors often affect the results causing poor correlation with objective measurements.[3–5] Also, when evaluating multiple forms of pain assessment in dogs, a significant amount of inter- and intraobserver variability has been noted.[6] A multivariate composite scale that comprises behaviors, interactions, responses, and clinical observations and weighs the results on the overall score may provide a more accurate portrayal of the patient's pain status.[7] The short-form GCPS has been described as a practical means of assessing acute postoperative pain and a useful tool in providing guidance in determining analgesic requirements.[8,9]

Although the evidence is mixed, some authors have reported that serum cortisol concentration may be used as a tool in the assessment of stress that may be associated with signs of pain in dogs.[10] Also, increased

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Firocoxib used in this study was provided by Merial.

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serum cortisol concentrations correlate with impaired limb function, suggesting that they could be used as a measure of pain in dogs.[11]

Pressure platform gait analysis has been used to provide objective data on limb function after orthopedic surgery in dogs in an effort to evaluate the efficacy of an NSAID for the treatment of signs of pain.[12] Similarly designed studies[13,14] have also been performed to measure limb function in cats after onychectomy to evaluate analgesic and surgical protocols. A pressure measurement walkway system[a] is a pressure platform analysis system that measures ground reaction forces.[14–16] One advantage to use of a pressure walkway (compared with a traditional force platform) is that a postoperative patient is not required to walk on an unsteady limb. Limb function data from all limbs can be gathered over a predetermined period (eg, 10 seconds) with dogs standing, and function of an individual limb can be evaluated or all of the limbs can be evaluated simultaneously.[17]

The purpose of the study reported here was to evaluate the analgesic efficacy and safety of tramadol and firocoxib in postoperative pain management following TPLO with GCPS, serum cortisol concentrations, and pressure platform analysis as tools for assessment. We hypothesized that firocoxib (when used alone) would be a more effective analgesic than orally administered tramadol (when used alone). We also hypothesized that if orally administered tramadol was an effective analgesic in dogs after TPLO, the combination of tramadol and firocoxib would provide the greatest analgesia (lowest pain scores, lowest cortisol concentrations, and greatest limb function in the operated limb).

## Materials and Methods

**Animals**—A randomized, masked, clinical investigation was conducted in 30 healthy adult client-owned dogs with a ruptured cranial cruciate ligament for which the owners chose caudal medial arthrotomy and TPLO with medial meniscal surgery (regardless of medial meniscus status) for treatment. To be included in the study, all dogs were required to weigh > 15 kg (33 lb), have normal findings on physical examination (with the exception of unilateral lameness and positive cranial drawer sign secondary to a torn cranial cruciate ligament), have results of preoperative CBC and serum biochemical analyses within reference ranges, and not have received corticosteroids for 30 days, NSAIDs for 5 days, or tramadol for 5 days prior to enrolling in the study. Dogs could be of any breed and either sex and had to be skeletally mature as determined on the basis of radiographs of the tibia. Informed owner consent was required for admission into the study; all study procedures were conducted following a protocol approved by the University of Minnesota Institutional Animal Care and Use Committee.

**Study groups**—Thirty dogs were randomly assigned to 3 groups to receive tramadol (oral tablet formulation, 4 to 5 mg/kg, q 8 h at 12 AM, 8 AM, and 4 PM beginning the afternoon before surgery), firocoxib[b] (oral tablet formulation, 5 mg/kg, q 24 h at 8 PM beginning the evening before surgery), or the tramadol and firocoxib dosages combined. An electronic spreadsheet program was used to create the randomization table. Administration of medications commenced the evening prior to surgery so each dog received a single treatment prior to surgery. Outcome measures included a subjective pain score (GCPS), serum cortisol concentration, and limb function (pressure platform gait analysis) of all 4 limbs during stance. Data from the outcome measures were collected the day prior to surgery (for baseline comparison) through the third day following surgery. A single veterinarian who was unaware of dog-group and group-drug assignments performed all outcome assessments.

**GCPS**—The GCPS pain scale comprised 6 behavioral categories with a maximum overall sum of 24 points: vocalization (4 points), attention to wound (5), mobility (5), response to touch (6), demeanor (5), and posture and activity (5). A single evaluator who was unaware of group and treatment assignments assessed dogs before handling for additional study procedures or treatments. Each dog was assessed at 10 time points. Scoring for signs of pain with the GCPS was performed at 4 PM the day before surgery, at 2 PM and 4 PM the day of surgery, and at 8 AM, 10 AM, and 2 PM on days after surgery.

**Limb function**—Limb function was measured simultaneously in all 4 limbs with a pressure measurement walkway system as described.[12] Prior to data acquisition, the walkway sensors were equilibrated and calibrated according to manufacturers' instructions. Limb function data were generated by collecting data from 3 valid trials beginning at 4 PM the afternoon prior to surgery for a baseline measurement and each morning (8 AM) on days 1, 2, and 3 following surgery immediately following GCPS assessment. A valid trial consisted of 10 seconds of standing with all feet weight-bearing on the walkway without extraneous movement from the dog. The first trial was used for acclimation of the dog to the procedure, and the mean of trials 2 and 3 was used to determine the dog's limb function for that assessment period. The percentage of the dog's body weight that was placed on the injured or operated limb was determined by comparing it with the total weight of the other 3 healthy limbs.

**Cortisol assay**—Venous blood samples were collected into a serum tube after all other assessments (GCPS and limb function evaluation [when applicable]) and were allowed to clot on ice for 30 minutes. The samples were centrifuged at 4°C for 15 minutes at 800 × g. The supernatant was frozen at –80°C, and a chemiluminescent immunoassay was used to determine serum cortisol concentration.[11]

**Adverse events**—Throughout the study, dogs were monitored for adverse events that may have been associated with use of study medications. In particular, sedation, hypersalivation, vomiting, and diarrhea were noted. If an adverse event occurred, it was classified as mild, moderate, or severe and as likely, possibly, or unlikely related to study drugs. If a dog developed a severe adverse event, it was removed from the study. The frequency of adverse events was compared among groups.

**Surgery**—Premedication prior to anesthesia consisted of acepromazine (0.02 to 0.03 mg/kg [0.009 to 0.014 mg/lb], IM) and morphine (1.0 mg/kg [0.45 mg/lb], IM). In an effort to provide uniform care to all dogs, anesthesia and surgery were performed the morning of day 0. Anesthesia was induced with propofol (1 to 6 mg/kg [0.45 to 2.73 mg/lb], IV, to effect) and maintained with isoflurane (≤ 2× minimum anesthetic concentration). Surgery included a caudomedial approach to the stifle joint, confirmation of a complete tear of the cranial cruciate ligament, and partial meniscectomy if the medial meniscus was torn or midbody medial meniscal release if the meniscus was visually normal, followed by the TPLO procedure. Postoperative analgesia was provided by administration of hydromorphone (0.05 mg/kg [0.023 mg/lb], SC) every 6 hours until midnight the evening of surgery.

**Rescue analgesia protocol**—Rescue analgesia consisted of administration of hydromorphone (0.05 mg/kg, SC) and was administered if the GCPS was ≥ 8 as determined by the investigator. If a dog required rescue analgesia, the dose would be recorded and monitoring would be resumed as scheduled without exclusion from the study. This allowed for documentation of opiate administration throughout the study. Aside from scheduled GCPS evaluations, dogs were monitored hourly by hospital staff with instructions to notify the investigator if the dog appeared to have signs of pain.

**Statistical analysis**—A 2-tailed $\chi^2$ test was used to compare the frequency of a GCPS score of ≥ 6 and ≥ 8 among groups and the frequency of serum cortisol concentrations > 1.6 and 3.5 µg/dL. Statistical analysis for GCPS values of ≥ 6 and ≥ 8 were tested because both values have been used in previous studies at our institution. Pearson correlation analysis was performed to evaluate the relationship among GCPS scores, plasma concentrations, and limb function. For cortisol concentrations and limb function, a 1-way ANOVA was performed at each time point to determine a group effect. If a group effect existed, pairwise *t* tests were performed to determine specific group significance under the Bonferroni correction. The time analysis was performed by means of paired *t* tests within a treatment group, and significance was established via the Bonferroni correction. A Kolmogorov-Smirnov distribution test was used to test for normal distribution of the data. Data are presented as mean ± SE. Values of $P \leq 0.05$ were considered significant.

## Results

The mean age of dogs enrolled in the study was 5.4 ± 2.25 years (range, 1 to 10 years). There was no significant difference in age among groups. Mean body weight of dogs was 34.65 ± 8.35 kg (range, 17 to 49.2 kg), and there was no significant difference in body weight among groups. The sex distribution within each group was as follows: 5 spayed females, 4 neutered males, and 1 sexually intact male in the tramadol group; 6 spayed females and 4 neutered males in the firocoxib group; and 7 spayed females and 3 neutered males in the tramadol-firocoxib combination group. There was nearly an equal distribution of affected limbs across the study (ie, left hind limb was affected in 16/30 dogs) and across study groups. Breed distribution consisted primarily of Labrador Retrievers (13/30 [43%]). Ten breeds of dogs were studied, and each study group included 5 breeds.

**GCPS**—A GCPS score ≥ 6 was observed in 8 of 10 dogs in the tramadol group, 4 of 10 dogs in the firocoxib group, and 6 of 10 in the group receiving both analgesics. The number of scores ≥ 6 for dogs in each group for the 90 postoperative assessments was 21 (23.33%) for the tramadol group, 6 (6.67%) for the firocoxib group, and 11 (12.22%) for the tramadol-firocoxib combined group. Dogs in the tramadol group had a score ≥ 6 significantly ($P = 0.004$) more often than dogs in the firocoxib group, but compared with the tramadol-firocoxib combination group, significance ($P = 0.079$) was not reached. No significant ($P = 0.31$) difference was present between the firocoxib and tramadol-firocoxib combination groups. A GCPS score ≥ 8 was observed in 4 of 10 dogs in the tramadol group, 1 of 10 dogs in the firocoxib group, and 1 of 10 in the group receiving both; each time a dog received a GCPS score ≥ 8, it received rescue medication. The number of scores ≥ 8 for dogs in each group for the 90 postoperative assessments was 8 (8.89%) for the tramadol group, 1 (1.11%) for the firocoxib group, and 1 (1.11%) for the tramadol-firocoxib combination group. The dogs in the tramadol group reached a score ≥ 8 and received rescue medication significantly ($P = 0.04$) more often than the dogs in the firocoxib group and the tramadol-firocoxib combination group. No significant difference was present between the firocoxib and tramadol-firocoxib combination groups. All rescue medications were given within 24 hours after surgery.

**Cortisol assay**—A significant change over time occurred in cortisol concentrations in all groups; however, no significant difference was found among groups (**Figure 1**). When considering all groups together, cor-

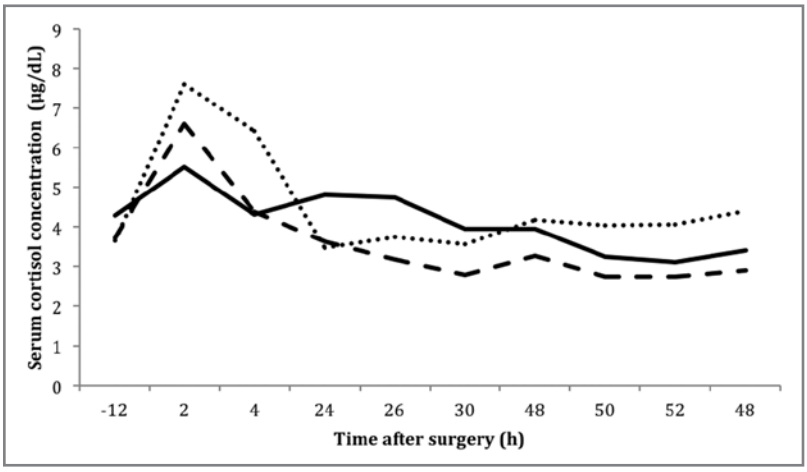


Figure 1—Mean serum cortisol concentrations of 30 adult client-owned dogs with unilateral cranial cruciate ligament disease that received tramadol (4 to 5 mg/kg, q 8 h at 12 AM, 8 AM, and 4 PM beginning the afternoon before surgery [solid line]), firocoxib (5 mg/kg, q 24 h at 8 PM beginning the evening before surgery [dashed line]), or the tramadol and firocoxib dosages combined (dotted line).

tisol concentration peaked at the first postoperative time period and remained high at the second evaluation the day after surgery. Although cortisol concentrations increased from the preoperative to first postoperative evaluation period in 67% of the dogs, the difference between the means of these 2 evaluations was not significant. Similarly, when comparing serum cortisol concentrations to a published threshold indicative of pain and lameness (1.6 µg/dL), there was no significant ($P$ = 0.07) difference in the frequency of dogs with values greater than this threshold between these 2 time periods (preoperative and first postoperative evaluation).[11] No correlation was found between GCPS scores and cortisol concentrations.

**Limb function**—Dogs in the tramadol group and the firocoxib group had a significant change in function of the operated limb over time **(Figure 2)**. The percentage of body weight applied by the operated (affected) limb decreased significantly from the day prior to surgery (day –1) to the day after surgery (day 1) in those 2 groups. Although the percentage of body weight borne by the operated limb also decreased after surgery for dogs in the tramadol-firocoxib combination group, the change was not significant. Dogs in the tramadol group put significantly less weight on their operated limb on days 1 ($P$ = 0.02) and 2 ($P$ = 0.05) after surgery. Dogs in the firocoxib group placed significantly ($P$ = 0.009) less weight on their operated limb only on day 1 after surgery. On all evaluation days, including day –1, dogs in the tramadol-firocoxib combination group put the highest percentage of their body weight on the affected or operated limb, compared with the other 2 groups. Limb function data had a significant ($P$ = 0.007) inverse correlation to GCPS score ($r$ = –0.27). During the postoperative assessments, limb function in dogs with a pain score < 6 (4.89% of total ground reaction force) was nearly twice that of dogs with a pain score ≥ 6 (2.75% of total ground reaction force).

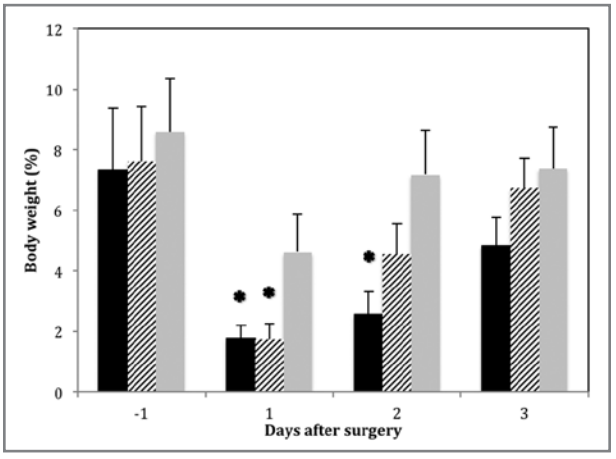


Figure 2—Mean ± SEM percentage of body weight placed on the operated limb, compared with the total amount of weight applied by all limbs during a 10-second period of standing in the same dogs as in Figure 1 that received tramadol (solid black bar), firocoxib (diagonal-striped bar), or tramadol and firocoxib dosages combined (gray bar) before and after surgery. *Significant ($P$ < 0.05) intragroup difference, compared with day –1 value.

**Adverse events**—Adverse effects such as vomiting, diarrhea, or severe sedation were not seen. One dog in the tramadol group was observed with a 1-minute episode of mild head tremors 2 days after surgery. This adverse event was noted as possibly associated with the study drug (tramadol); it resolved without additional treatment, and drug treatment continued as scheduled without further incident.

## Discussion

Providing satisfactory perioperative analgesia will remain challenging given the limitations regarding assessment of pain in veterinary patients. This challenge is increased when medications that may or may not provide analgesia become popularized before they are scientifically investigated. Results of this clinical study provided evidence that tramadol given alone was not as effective an analgesic after TPLO as an FDA-approved NSAID given alone.

Patient signalment among groups was similar regarding age, body weight, and sex, but this study did include many breeds of dogs. Empirically, different breeds have different behaviors when exposed to stressful conditions, analgesic or sedative drugs, and pain. Considering that the GCPS is based solely on interpretation of patient behavior, it would have been ideal to control breeds among groups in this study. Each group did include an equal number (5) of breeds. In addition, each dog's experiences prior to enrollment in this study may have influenced behavior. For example, a dog that had been to a hospital several times or had undergone general anesthesia and surgery prior to enrollment might have different behaviors than a dog of similar signalment that had not had those experiences. We did not evaluate information regarding patient anesthesia or surgical history in this study. Similarly, the personal experiences of the persons interpreting clinical signs and completing the GCPS may influence scores. We did attempt to control for variation and bias associated with the pain evaluator by having the same individual (DD) perform all pain evaluations and rescue decisions and having the pain evaluator unaware of patient-group assignment and group-drug assignment. Similarly, all technical staff who provided patient care or communicated with the pain evaluator were unaware of study group assignments. All analgesic drugs were given by 1 of 2 veterinary technicians who were aware of assignments but did not perform additional patient care. Analgesia was provided when a GCPS score was ≥ 8. One could argue that analgesia should have been given with a different GCPS threshold; however, previous studies have suggested consideration for additional analgesia when the GCPS score is ≥ 4,[18] > 6,[19] or > 8.[20]

Results of the present study indicated that dogs in the tramadol group had a GCPS score ≥ 6 and ≥ 8 more frequently than did dogs in the other groups. From this, one could conclude that tramadol given alone provided less effective analgesia than firocoxib given alone. Similarly, considering that there was no significant difference in weight bearing after surgery between the firocoxib group and the tramadol-firocoxib combination group, one could conclude that tramadol did not provide any additional analgesic relief, compared

with firocoxib alone. These findings could be explained by tramadol providing inferior analgesia or the anti-inflammatory effect of firocoxib improving its analgesic response for this outcome measure.

There were no significant differences among groups for serum cortisol concentrations. We were not surprised by this, given the variety of dogs studied, the likely differences in the dogs' backgrounds, and the number of dogs per group. Nonetheless, we chose to evaluate cortisol concentration in an effort to evaluate all possible factors and determine whether it should be routinely considered as an objective outcome measure for clinical pain studies. The data provided some evidence that serum cortisol concentration increased soon after surgery but returned to reference range within 24 hours. Although this could be seen graphically in the mean data for all 3 groups, to determine a significant change over time, group data had to be combined. Given the timing of the increase in cortisol concentrations (within hours after general anesthesia and surgery) and the fact that cortisol concentrations did not correlate with pain scores, it is difficult to be convinced that the change was solely because of pain. A control group in which dogs only received the anesthetic and analgesic medication would have made for a useful comparison but was beyond the scope of this clinical investigation. The variation documented in this study provides some direction for future investigations. This outcome measure was also chosen because plasma cortisol concentrations have a positive correlation with stress in dogs.[21] However, cortisol concentrations may be affected by anticipatory stress or anxiety associated with venipuncture.[22] In addition, samples for cortisol concentration determination were obtained after performing the gait analysis and GCPS; the results may have been different if the samples had been collected before performing those tests. The tests were performed in this order because the GCPS and gait analysis were deemed to have higher priority and may have been influenced by the stress of blood sampling. A central line was not placed for regular blood sampling because this may have contributed to additional stress and increased variance in the results. Alternative methods to consider for decreasing stress in future studies may include measuring urinary or salivary cortisol concentrations.[23–25] Many environmental variables that may also skew the results include anticipation of being approached, kenneling, breed, age, temperament, and frequency of feeding.[26,27] In addition, other studies[28] that used cortisol concentration as a measure of pain assessment did not always find a significant correlation, thereby indicating variability and inconsistent results.

Pressure platform gait analysis has advantages over force platform gait analysis in terms of ease of use for a postoperative patient that has difficulty ambulating on an operated limb. This outcome measure was used because the authors believe that use of the operated limb after this particular knee surgery is a reasonable estimate of patient pain. Given the difficulty in measuring signs of pain in animals, it makes sense to use both subjective and objective outcome measures when possible. In this study, the GCPS (subjective) and limb function (objective) had a significant inverse correlation, and when dogs had a GCPS score ≥ 6, their limb function was only 56.2% of that when dogs had a GCPS score < 6. Use of the operated limb was similar to the GCPS findings in that the dogs treated with tramadol alone used their operated limb the least for the greatest amount of time. This suggested that the dogs treated with tramadol alone were in the greatest discomfort. Because dogs in the tramadol group also received more rescue analgesics, the findings may underestimate the difference between groups; in effect, if no rescue analgesic was provided, the dogs receiving tramadol alone would have had even worse limb function and greater GCPS scores, compared with the other groups. One finding that differed from the GCPS data was that the dogs that received both tramadol and firocoxib had the greatest limb function after surgery. This cast some doubt on a conclusion that tramadol has no added analgesic benefit over firocoxib.

Firocoxib is a COX-2 selective, COX-1 sparing NSAID specifically developed for veterinary use that has been proven to provide effective relief of signs of pain after orthopedic surgery and in the treatment of osteoarthritis.[29–31] Benefits to its use over some other NSAIDS may include ease of administration (once daily) as well as decreased risk of adverse reactions associated with the gastrointestinal tract, attributable to sparing of the COX-1 enzyme.[30] In addition, firocoxib provided improved relief of signs of pain in an experimental sodium urate–induced synovitis study, compared with other NSAIDs.[32]

Tramadol is frequently used for pain management in veterinary medicine, yet its clinical safety and efficacy profile is limited. This may be because of its low bioavailability in the formulation used for oral administration. Tramadol's major metabolite, O-desmethyltramadol, is more potent at the μ-receptor than the parent drug but may be metabolized faster in dogs, compared with humans.[33] The cause for the difference in metabolite concentrations in dogs versus humans is suspected to be a result of a different cytochrome P450 ultrametabolizer.[1,34] Further studies to identify the specific cytochrome P450 associated with tramadol metabolism would be beneficial in evaluating its pharmacokinetics. Plasma and urine analyses of the metabolites after oral administration of immediate-release tablets indicate that O-desmethyltramadol is present only in negligible quantities.[35] Although low plasma concentrations were detected, some limited antinociceptive effects have been reported in Greyhounds.[34] Compared with codeine and ketoprofen, used alone or in combination, no significant differences were found in terms of changes of physiologic variables, serum cortisol concentration, and serum interleukin-6 concentration as indicators of pain.[36] Compared with morphine administration for controlling postoperative pain associated with ovariohysterectomy in dogs, no difference was detected.[37]

A multimodal approach for analgesia is beneficial because of drug additive or synergistic effects, with concomitant reduction of adverse effects associated with lower doses of analgesics.[38] Specifically, the analgesic efficacy of an opioid in combination with an NSAID has been studied and is greater than when each

is administered alone in preventing hyperalgesia following surgery.[39–41] The preoperative use of analgesics has also been studied to help prevent pain wind-up and decrease the amount of postoperative pain.[40,41] In the present study, we included a group with a multimodal approach but elected not to use decreased drug doses. Although the limb function data suggested that the multimodal approach (tramadol-firocoxib combined) provided the greatest limb function, the subjective pain scores did not confirm this. Unfortunately, this leaves some conclusions up for speculation. One contribution to this uncertainty is that only 10 dogs/group were included in this study. However, considering that significantly fewer dogs in the firocoxib group had high pain scores (GCPS ≤ 6 or ≤ 8) and they had decreased limb function for fewer days, compared with dogs in the tramadol group, we accept the hypothesis that firocoxib (when used alone) is a more effective analgesic than orally administered tramadol (when used alone).

a. I-scan pressure measurement walkway system, TekScan Inc, Boston, Mass.
b. PREVICOX, Merial, Atlanta, Ga.

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