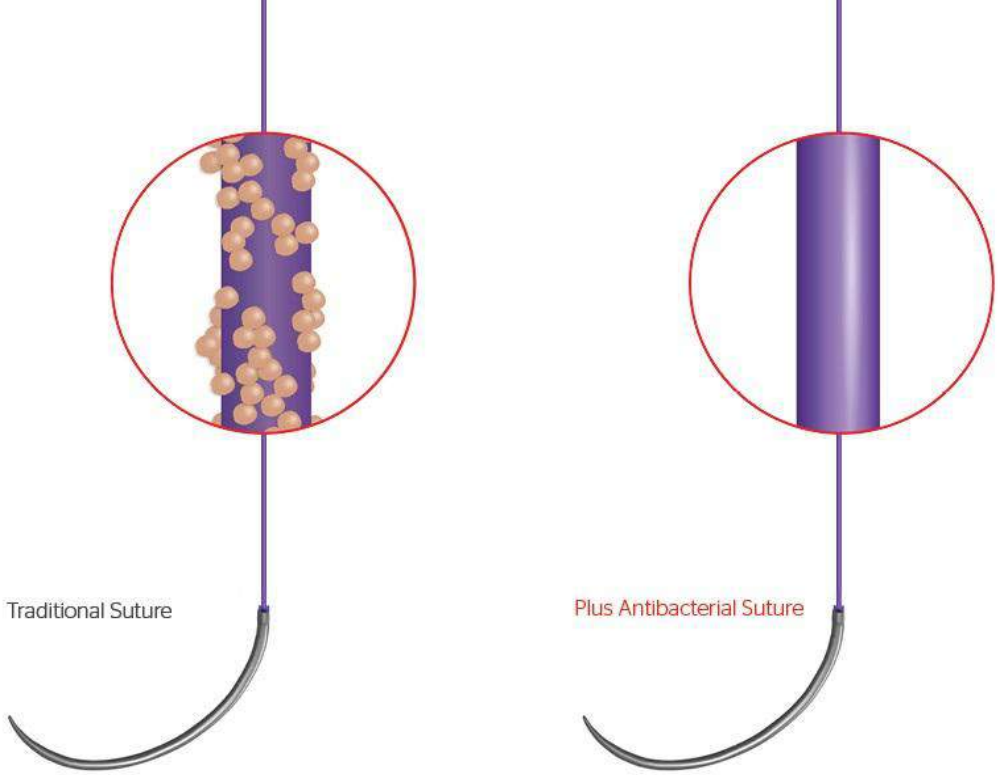

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ORIGINAL ARTICLE

Once daily oral extended-release hydrocodone as analgesia following tibial plateau leveling osteotomy in dogs

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Abstract

Objective: To determine the efficacy of oral extended-release hydrocodone compared with oral firocoxib for analgesia following tibial plateau leveling osteotomy surgery in dogs in a hospital setting.

Study design: Prospective, randomized, blinded, clinical trial.

Animals: Thirty-six client-owned dogs weighing 25-43 kg with unilateral hindlimb lameness and cranial cruciate ligament rupture.

Methods: Dogs were assigned to 1 of 2 groups (n = 18/group). Group 1 received hydrocodone 3 mg/kg orally every 24 hours, and group 2 received firocoxib 5 mg/kg orally every 24 hours. Both hydrocodone and firocoxib (according to group assignment) were provided as preemptive analgesia 10 hours before induction to anesthesia and then every 24 hours for the remainder of the study period The level of analgesia was compared between treatments on the basis of a modified Glasgow Composite Pain Score (mGCPS) in each dog, the number of dogs requiring rescue analgesia (hydromorphone 0.05 mg/kg subcutaneously), pressure platform stance data, and number of adverse events.

Results: Nine of 18 dogs that received hydrocodone and 2/18 dogs that received firocoxib had an mGCPS $\geq$6 ($P = .02$). Two dogs had an mGCPS $\geq$6 three times, and 1 had an mGCPS $\geq$6 two times; all 3 of these dogs were in the hydrocodone group. Average postoperative peak pressure placed on the affected limb was lower in dogs that received hydrocodone ($P = .01$). Regurgitation and decreased appetite were more common in the dogs that received hydrocodone.

Conclusion: Dogs that were treated with hydrocodone exhibited higher pain scores and lower limb function than dogs treated with firocoxib under the conditions of our study.

Clinical significance: Our results do not provide evidence to justify the administration of extended-release hydrocodone at 3 mg/kg orally every 24 hours rather than firocoxib at 5 mg/kg orally every 24 hours in dogs undergoing tibial plateau leveling osteotomy.

1 | INTRODUCTION

Orally delivered pain control in the dog remains challenging because of limited canine-specific research evaluating potential medications, differences in metabolism of drugs between species, and imprecise pain evaluation in dogs. Nonsteroidal anti-inflammatory drugs (NSAID) are US Food and Drug Administration (FDA) approved as perioperative analgesics and have been found to improve limb function in clinical perioperative pain studies.[1-4] However, many dogs have contraindications to NSAID use, and a viable alternative orally delivered pain control is required in the dog.

Hydrocodone is a schedule II μ-opioid agonist and a commonly used analgesic and antitussive in man. Historically in veterinary medicine, immediate release hydrocodone has been used as a potent antitussive agent and less frequently as an oral opioid analgesic. It is variably metabolized to hydromorphone in many species, including dogs, and is equipotent to morphine in producing opiate effects.[5] Immediate release hydrocodone has been found to be more bioavailable after oral administration in the dog (39%) compared with codeine (4%-7%) and morphine (5%), and its bioavailability is much less variable than that of tramadol.[6-10] In addition, hydromorphone is an active metabolite that has been consistently found present in clinically relevant concentrations after oral administration of hydrocodone in dogs.[11-13] The use of extended-release hydrocodone that does not contain acetaminophen in veterinary medicine may reduce drug abuse potential, increase owner compliance, and avoid hepatotoxic adverse events.[14-16] Hydrocodone may prove to be an improved oral perioperative analgesic alternative for dogs with contraindications to NSAID use.

Little scientific evidence supports oral hydrocodone use as an effective perioperative analgesic in the dog. Benitez et al[17] found that hydrocodone–acetaminophen at a dosage of 0.5-0.6 mg/kg hydrocodone every 8 hours orally was equivalent to tramadol hydrochloride at 5-7 mg/kg every 8 hours orally in postoperative pain control, assessed by a modified Glasgow Composite Pain Score (mGCPS), in dogs undergoing orthopedic surgery. However, because of the study design (no FDA-approved positive control or placebo group) and the potential benefits of acetaminophen, there is still uncertainty whether oral hydrocodone is an effective analgesic in the dog. To the best of our knowledge, no clinical studies have evaluated the efficacy of orally administered extended-release pure hydrocodone analgesic for treatment of postoperative pain in dogs.[17]

Effective postoperative pain management is widely accepted as adequate patient care in veterinary medicine. Unfortunately, pain assessment can be difficult in animals. Pain assessment rating systems such as the simple descriptive scale, the visual analogue scale, and the numeric rating scale have been employed in veterinary medicine in an attempt to improve consistent pain assessment in veterinary patients.[18-21] The only validated method for evaluating signs of postoperative pain in dogs is the mGCPS.[22-24] However, these rating systems are subjective, making interpretation challenging. It may be ideal to complement the mGCPS with an alternative objective outcome measure that estimates the level of perioperative pain in dogs and cats via the measurement of limb function after limb surgery with pressure platforms.[1,2,25-27]

The objective of this study was to evaluate the efficacy of oral extended-release hydrocodone compared with oral firocoxib as a perioperative analgesic following tibial plateau leveling osteotomy (TPLO) surgery in dogs in a hospital setting. The level of analgesia provided by oral hydrocodone or firocoxib was determined by comparing mGCPS, number of dogs requiring rescue analgesia, and pressure platform stance data. The number of adverse events between groups was also used to determine efficacy. Our null hypothesis was that hydrocodone bitartrate (extended release 3 mg/kg orally every 24 hours) and firocoxib (5 mg/kg orally every 24 hours) would provide the same analgesic effect in dogs following TPLO surgery.

2 | MATERIALS AND METHODS

2.1 | Animals

A prospective, randomized, blinded clinical investigation was conducted in 36 client-owned dogs. Dogs weighing 25-43 kg that were presented to the University of Minnesota Veterinary Medical Center with unilateral hindlimb lameness and a diagnosis of cranial cruciate ligament rupture were enrolled in the study. For final inclusion in the study, the dogs had to be clinically healthy, American Society of Anesthesiology status II, with no outstanding abnormalities other than a diagnosis of unilateral cranial cruciate ligament rupture determined by physical examination or presurgical complete blood count and serum chemistry profile. Physical examination was conducted by a veterinarian. Physical examination results were recorded on a standardized form according to facility standard practice. Preoperative radiographs were performed of the affected stifle which had to show that the dog was skeletally mature as verified by radiographic closure of the distal femoral physis of the affected stifle. The dog could not have any history of gastrointestinal problems with hydrocodone or NSAID or any history of vomiting, diarrhea, or anorexia for the past 14 days. Additionally, the dog could not have received NSAID, steroids, tramadol, amantadine, gabapentin, or opioids for 3 days prior to enrollment in the study. Dogs were excluded if they were pregnant, had neurological impairment, were aggressive, or had received a routine vaccination within 1 week of the start of data collection. Dogs could be of any breed and either sex. Informed owner consent was required for admission to the study. All study procedures were conducted according to a protocol approved by the University of Minnesota Institutional Animal Care and Use Committee.

2.2 | Study groups

Thirty-six dogs were randomly assigned to 2 groups (n = 18/group) by using Excel (Microsoft, Redmond, Washington). Group sizes were determined by using available data from previously published research that had used similar methods.[1,2] Group 1 received extended-release hydrocodone bitartrate film-coated tablets (Hysingla ER; Purdue Pharma,

TABLE 1 Data collection and treatment schedule

Day	Hour	CBC/Chem	Surgery	mGCPS	Pressure platform	Firocoxib (n = 18)	Hydrocodone (n = 18)
−1	<8 PM	X		X	X		
	10 PM					X	X
0	8 AM		X				
	2 PM			X			
	8 PM			X			
	10 PM					X	X
1	8 AM			X	X		
	2 PM			X			
	8 PM			X			
	10 PM					X	X
2	8 AM			X	X		
	2 PM			X			
	8 PM			X			
	10 PM					X	X
3	8 AM			X	X		

CBC, complete blood count; Chem, chemistry profile; mGCPS, modified Glasgow Composite Pain Score; X, data collected or treatment performed.

Stamford, Connecticut) 3 mg/kg (2.6-3.2 mg/kg) orally every 24 hours. Group 2 received firocoxib (Previcox; Merial, Duluth, Georgia) 5 mg/kg (3.5-6.8 mg/kg) orally every 24 hours. Both hydrocodone and firocoxib (according to group assignment) were provided as preemptive analgesia 10 hours before induction to anesthesia and then every 24 hours for the remainder of the study period (Table 1). Two investigators that were blinded to the treatment groups performed regularly scheduled pain evaluations (Table 1). Criteria for rescue analgesia included scoring ≥6 on the mGCPS.[2,24,28-30] Rescue analgesia consisted of administration of hydromorphone (0.05 mg/kg subcutaneously) as previously described.[2] Dogs were closely monitored after surgery in a postanesthetic recovery unit until they were able to walk from the recovery area to the wards. In addition, beyond the scheduled mGCPS assessments, dogs received standard of care assessments on an hourly basis while hospitalized. If a dog appeared to be experiencing pain between scheduled study mGCPS scoring times, the study observers were contacted so they could perform an mGCPS assessment and provide rescue analgesic as required. When a dog scored ≥6, the dog received rescue analgesia and was reevaluated hourly and treated as required until the mGCPS no longer remained ≥6. The scores used for intervention were based on cutoffs by a previous study.[24] The number of dogs and doses per dog requiring rescue analgesia was documented. Dogs that required rescue analgesia remained in the study, were evaluated for adverse events, and were used to determine whether the frequency of rescue analgesia required differed between groups. The mGCPS and pressure platform stance data were recorded until the time of patient discharge (day 3).

Because of the difficulty of measuring pain in veterinary patients, a more objective outcome measure was used in combination with the mGCPS to evaluate postoperative pain. Pressure platform stance data were measured simultaneously in all 4 limbs with a walkway gait analysis system (Tekscan, South Boston, Massachusetts) as previously described.[1,31] The walkway was equilibrated and calibrated according to manufacturer specifications prior to each instance of data acquisition.[31-33] Pressure platform data were collected from 3 valid trials prior to the first dose of study drug for a baseline measurement and then daily (8 AM) for 3 days after surgery, as described in Table 1. A valid trial consisted of 10 seconds of the dog standing with all weight-bearing feet on the walkway without extraneous movement. The percentage of the dog's body weight that was placed on each limb was determined by comparing it with the total weight of the dog.

2.3 | Adverse events

Dogs were monitored on an hourly basis for adverse events that may have been associated with the use of study medications. Adverse events were defined as excessive sedation (stuporous or altered mental status in which the dog is arousable only with vigorous or unpleasant stimulation), inappetence, hypersalivation, vomiting, regurgitation, diarrhea, and urinary retention.[34] Appetite was assessed by the number of meals completely consumed that had been

presented to the dog. The number of hours to first urination after surgery was documented to assess for urinary retention. Any observed changes in behavior or adverse events that were noted were recorded as mild, moderate, or severe and whether they were unlikely, possibly, or likely related to the test article.

2.4 | Surgery and anesthesia

All dogs were scheduled to have anesthesia and surgery the morning of day 0 in an effort to provide uniform care. Dogs received premedication with acepromazine (0.02 mg/kg intramuscularly [IM]) and morphine (0.5 mg/kg IM). Induction of anesthesia was with propofol (1-6 mg/kg) administered IV to effect. Cephalexin (22 mg/kg IV) was administered 20 minutes prior to surgery and then every 90 minutes for the duration of the procedure. Maintenance of anesthesia was with isoflurane in oxygen delivered at 2× minimum alveolar concentration or less and a fentanyl constant rate infusion (10 μg/kg/h IV) to maintain appropriate anesthetic depth. Surgery included either a caudomedial or a medial parapatellar approach to the stifle joint, a partial meniscectomy if the medial meniscus was torn, or a mid-body medial meniscal release as dictated by the surgeon, followed by the TPLO procedure. Hydromorphone (0.05 mg/kg IV) was given once immediately postoperatively. Postoperative cephalexin (30 mg/kg orally every 12 hours) was prescribed according to clinician preference. Postoperative pain score assessments with the mGCPS were started at 2 PM on the day of surgery (Table 1).

2.5 | Statistical analysis

To test for a difference in rescue rates between the 2 treatments, we fit a logistic regression on rescue with treatment as the predictor. To test for differences in side effects, we fit logistic regressions (for vomiting, regurgitation, and diarrhea) and linear regressions (for appetite and urination hours) with treatment as the predictor and also antibiotic use as a covariate. Terms in logistic models with quasi-complete separation were tested by using a likelihood ratio test.

To test for a difference in percentage weight placed on an affected leg, we fit a mixed model on the peak average percentage (averaged over 3 measurements) with treatment, day, and their interaction and a random effect for individual. Covariates for arthrotomy type and surgeon were also tested but were included in the model only if they impacted the average peak pressure. Day was treated as a categorical variable, with baseline, day 1, day 2, and day 3. Differences in least squares means from baseline were computed for each day and for the average of the 3 days.

3 | RESULTS

Thirty-six dogs met the inclusion criteria and were enrolled in the study. Eighteen dogs were randomly assigned to each group. The signalment data for each group are defined in Table 2. There was no difference in sex, affected hindlimb, or weight in either group. However, there was a difference in age; the mean age of 4.1 years in the hydrocodone group was less than the mean age of 6.3 years in the firocoxib group ($P = .02$).

Preoperative mGCPS for all dogs was less than 6 (range, 1-4). After surgery, an mGCPS $\geq$6 was documented in 9 of 18 (50%) dogs in the hydrocodone group and in 2 of 18 (11%) dogs in the firocoxib group. Thus, dogs in the hydrocodone group required rescue analgesia more than the dogs in the firocoxib group ($P = .02$). The range of pain scores for dogs requiring rescue analgesia was 6-12 out of a maximum score of 24. Two dogs had an mGCPS $\geq$6 three times, and 1 dog had an mGCPS $\geq$6 two times; all 3 of these dogs were in the hydrocodone group. All but 2 dogs required the rescue analgesia prior to the second administration of the study drug. Details of the timing of rescue and the associated mGCPS are listed in Table 3.

Pressure platform measurements were collected on days −1, 1, 2, and 3 for all dogs (Figure 1). There was no significant difference in average peak pressure placed on the affected hindlimb between groups before surgery (3.77% for hydrocodone, 3.98% for firocoxib; 95% CI for difference −2.15%, 1.73%, $P = .83$). On average during the 3 postoperative days, dogs in the hydrocodone group placed less weight on their treated leg compared with the dogs in the firocoxib group (0.70% for hydrocodone, 2.97% for firocoxib; 95% CI for difference compared with difference of baseline pressure before surgery 0.42%, 3.70%, $P = .014$). There was no difference between groups for the 3 postoperative days. The type of arthrotomy and the individual surgeon performing the procedure were analyzed as covariates and were not found to impact the average peak pressure placed in the affected hindlimb postoperatively in either group.

The the number of dogs that had excessive sedation, hypersalivation, vomiting, and diarrhea was not different between each group (Table 4). The number of meals completely consumed by each dog during the study period was used to assess appetite. According to this definition, appetite was reduced in dogs that received hydrocodone compared with dogs that received firocoxib ($P = .02$). Dogs were more likely to have an episode of regurgitation in the hydrocodone group compared with the firocoxib group ($P = .01$). The use of cephalexin postoperatively was not found to be a precursor for adverse events of reduced appetite, vomiting, diarrhea, and regurgitation in either group. There was no difference between the 2 groups on the time until the first urination postoperatively ($P = .85$).

TABLE 2 Signalment data of both study groups[a]

Variables	Group 1: hydrocodone (n = 18)	Group 2: firocoxib (n = 18)
Sex		
MN	6	5
MI	1	0
FS	11	13
FI	0	0
Affected limb		
Left	11	9
Right	7	9
Age, y, mean (range)	4.1 (1-10)	6.3 (2-11)
Weight, kg, mean (range)	34.5 (27.2-41.0)	31.8 (24.5-42.4)
Breed (n)		
	Labrador retriever (9)	Mixed breed (5)
	Rottweiler (3)	Golden retriever (4)
	Mixed breed (2)	Labrador retriever (4)
	German shepherd dog (2)	Black mouth cur (1)
	English setter (1)	Alaskan husky (1)
	American bulldog (1)	Australian cattle dog (1)
		German shepherd dog (1)
		Staffordshire bull terrier (1)

FI. intact female; FS, spayed female; MI, intact male; NM, neutered male.
[a]There was a significant difference in mean age between groups ($P = .02$).

4 | DISCUSSION

The results of this clinical study provide strong evidence that extended-release hydrocodone bitartrate at a dosage of 3 mg/kg given 10 hours prior to surgery orally and every 24 hours was inferior to the analgesia provided by firocoxib at a dosage of 5 mg/kg given 10 hours prior to surgery orally and every 24 hours, as assessed by the number of dogs requiring rescue analgesia and the amount of weight placed on the affected hindlimb postoperatively. From these results, we

TABLE 3 Rescue analgesia timing during the study period and mGCPS associated with the rescue event[a]

Dog	Study drug	Day −1	Day 0	Day 1	Day 2	Day 3
1	H		1500 (7)			
2	H				0800 (7)	
3	F		1400 (6)			
4	H		2000 (8)			
5	H		1250 (12) 2000 (8)			
6	H		1600 (6)			
7	H		2000 (11)			
8	F		2035 (7)			
9	H		2000 (6)			
10	H		1825 (10) 2000 (11)	1400 (9)		
11	H		1310 (9) 1400 (9) 1910 (7)			

F, firocoxib; H, hydrocodone.
[a]Times are in military time. The mGCPS is in parentheses after the associated time of rescue.

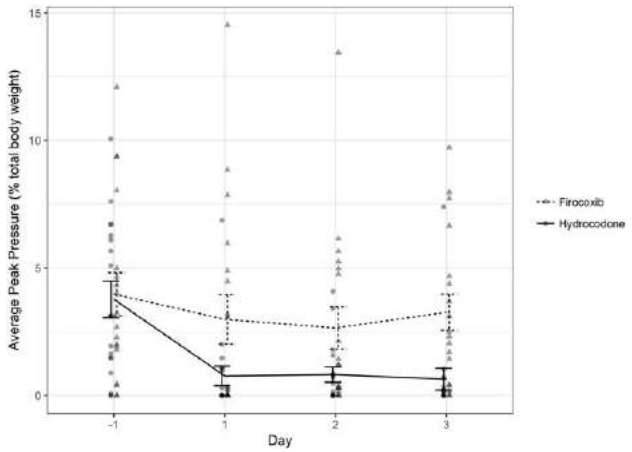

FIGURE 1 Average peak pressure in the affected limb (% body weight) on each day of the study period for dogs that received perioperative hydrocodone and firocoxib. Dots and triangles represent the average peak pressure of the affected limb of an individual clinical case. Bold and dashed lines represent the average peak pressure in the affected limb of the dogs in each group during the study period. Dots and bold line are associated with hydrocodone cases. Triangles and dashed line are associated with firocoxib cases. SE bars represent ± 1 SE. Dogs in the hydrocodone group placed less weight on their treated leg compared with dogs in the firocoxib group, as assessed by the difference in least squares means from baseline for the average of the 3 postoperative days ($P = .01$)

reject our null hypothesis that hydrocodone bitartrate (extended-release film-coated tablets 3 mg/kg orally every 24 hours) and firocoxib (5 mg/kg orally every 24 hours) would provide the same analgesic effect in dogs following TPLO surgery. In addition, dogs that received hydrocodone had statistically more regurgitation and decreased appetite compared with those that received firocoxib.

Results of the present study indicate that dogs in the hydrocodone group had an mGCPS >6 significantly more frequently than dogs in the firocoxib group ($P = .02$). In addition, only dogs in the hydrocodone group required multiple doses of rescue analgesia. From this, one could conclude that oral extended-release hydrocodone provides less effective analgesia than oral firocoxib. The fact that some dogs required rescue analgesia multiple times could also indicate that the rescue protocol was not adequate in all dogs[35] or that these particular dogs had a lower pain tolerance than other dogs in the study.

Increased use of the treated limb in the dogs that received firocoxib correlated with the results of the mGCPS in that dogs that received firocoxib were less likely to receive rescue analgesia, suggesting that the dogs that had received hydrocodone were experiencing more discomfort. Because dogs that had been given hydrocodone received more rescue analgesia, the findings in this study may actually underestimate the difference between the 2 groups, and dogs that had received hydrocodone may have had even worse limb function than dogs that had received firocoxib. A limitation of the pressure platform is that it is a static, rather than a dynamic, evaluation of limb function. In addition, there is variability between the individual trials used to obtain an average as the dog tires from standing.

Opiates activate μ receptors within the intestinal tract; adverse effects with opioids have been well documented and include sedation, nausea, vomiting, delayed gastric emptying, and urine retention.[34,36] Dogs that received hydrocodone in this study were found to have a reduced appetite and a higher risk of regurgitation than those that received firocoxib. The use of rescue analgesia and cephalexin were not found to be precursors for these adverse events. Reduced appetite and regurgitation are consistent with reported side effects associated with opioid administration. However, other factors such as patient temperament, recent anesthesia, anxiety within a hospital setting, or increased pain could also be associated with these adverse events.

Because there are no reports of pharmacokinetics of extended-release hydrocodone in the dog, and pharmacokinetics was not within the scope of this study, conclusions should be limited to the protocol described. The extended-release hydrocodone bitartrate film-coated tablet used in this study was selected because it was the only commercially available 24-hour form available at the time. A median T_{max} of 14-16 hours and a mean terminal half-life ranging from 7 to 9 hours occurred in man for all available dose strengths when given orally.[37] Perhaps this extended-release formula does not have the same rate of release in dogs as it does in man. To the best of our knowledge, there are no data on film-coated tablet drug release in dogs compared with man. However, in this study, only 2 of the 9 dogs required rescue analgesia after the first postoperative oral dose of hydrocodone. These findings, in combination with the reported

TABLE 4 Number of dogs with adverse events (n = 18/group)[a]

Adverse events	Group 1: hydrocodone	Group 2: firocoxib	*P* value[b]
Excessive sedation, n	0	0	1
Hypersalivation, n	0	0	1
Average meals consumed, %[a]	56	77	.02
Vomiting, n	1	3	.33
Diarrhea, n	2	2	.90
Regurgitation, n	4	0	.01
Mean time to first urination, h (range)	22.7 (9-48)	23.6 (9-37)	.85

[a]Average % of meals consumed is based on the number of complete consumption of meals offered per dog.
[b]$P \leq .05$ was considered significant.

adverse events during the study, may suggest that some analgesic activity is associated with the extended-release formula of hydrocodone, but not necessarily over the full 24-hour period.

Multiple studies have found that, in preventing hyperalgesia postoperatively, analgesic efficacy of an opioid in combination with an NSAID is greater than when each is administered separately.[38,39] In addition, a multimodal approach for analgesia is beneficial because of a reduction in adverse effects associated with lower doses of analgesics because of drug additive or synergistic effects.[40] This study did not compare the postoperative analgesic effect of concurrent administration of hydrocodone and firocoxib in dogs; therefore, no conclusions can be made about synergistic effects of the 2 drugs given together.

The results of this study do not objectively provide evidence for a benefit to the sole administration of this formulation of oral extended-release hydrocodone at a dosage of 3 mg/kg orally every 24 hours in perioperative pain control associated with a TPLO procedure in dogs. Additional research is required to discover a safe and effective oral analgesic for dogs that can complement or serve as an alternate to NSAID.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this report.

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