Evaluation of subcutaneous and oral administration of robenacoxib and meloxicam for the treatment of acute pain and inflammation associated with orthopedic surgery in dogs

Philippe Gruet, DVM; Wolfgang Seewald, PhD; Jonathan N. King, BVSc, PhD

Objective—To assess efficacy and tolerability of robenacoxib for control of pain and inflammation in dogs undergoing orthopedic surgery.

Animals—140 client-owned dogs.

Procedures—A multicenter, prospective, randomized, blinded field trial was conducted to compare robenacoxib (97 dogs) and meloxicam (43 dogs). After randomization, each dog received an initial dose (robenacoxib, 2 mg/kg; meloxicam, 0.2 mg/kg) via SC injection before surgery and daily doses (robenacoxib, 1 to 2 mg/kg; meloxicam, 0.1 mg/kg) administered orally for up to 15 days after surgery. Efficacy was assessed by veterinarians and owners via numeric rating scales and visual analogue scales. Safety was assessed on the basis of reported adverse events, clinical signs, results of hematologic and biochemical analyses, and buccal mucosa bleeding times.

Results—Treatment groups were balanced with respect to baseline and demographic data. Both treatments provided similar adequate pain control, as assessed with a modified Glasgow pain scale as the primary end point and supported by secondary end points in evaluations conducted by veterinarians and owners. For the primary end point, the ratio of the reciprocal of the scores for robenacoxib to meloxicam was 1.16 (95% confidence interval, 0.98 to 1.37). No dogs required rescue analgesia. Both treatments were associated with only minor adverse events, which were not necessarily related to the administered treatments and did not affect mucosal bleeding times.

Conclusions and Clinical Relevance—Robenacoxib provided efficacy and tolerability similar to those of meloxicam for the management of perioperative pain and inflammation in dogs undergoing orthopedic surgery. (*Am J Vet Res* 2011;72:184–193)

Orthopedic surgery in dogs is commonly associated with severe postoperative pain and inflammation. Therefore, it is essential to provide effective analgesia during the immediate postoperative period and for several days or weeks thereafter.[1,2] Moreover, effective pain control may result in a more rapid recovery and return to anticipated function. Of the available classes of analgesics available for use in dogs, only those of the opioid and NSAID classes have the appropriate pharmacological and safety profiles for use during the postoperative period.[1] Opioid drugs can provide excellent analgesia during the immediate postoperative period, but the relatively short duration of action and potential adverse effects of available opioid drugs generally limit their use to the first 24 to 48 hours after completion of surgery. The NSAIDs have acceptable safety and sufficiently long durations of action (ie, administered once daily) to provide for the relief of pain and inflammation for several days or weeks after surgery. Furthermore, there are reports[3,4] that NSAIDs are more effective than are opioids for relief of surgery-related pain.

Robenacoxib is an NSAID with some properties (most notably, a fast onset of action and a high safety index) that may be of benefit for use in the management of perioperative pain and inflammation.[5,6] At recommended dosages (up to 2 mg/kg), robenacoxib inhibits COX-2 but spares COX-1 in dogs, which should minimize the potential for causing damage to the gas-

Abbreviations

CI	Confidence interval
COX	Cyclooxygenase
NRS	Numeric rating scale
VAS	Visual analogue scale

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From Novartis Santé Animale SAS, F-92845 Rueil-Malmaison, France (Gruet); and Novartis Animal Health Inc, CH-4058 Basel, Switzerland (Seewald, King). Dr. Gruet's present address is Novartis Santé Animale SAS, 14, Bd Richelieu – BP 430, F-92845 Rueil Malmaison Cedex, France.
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Address correspondence to Dr. Gruet (philippe.gruet@novartis.com).

trointestinal tract and interfering with blood clotting pathways.[5,6] In addition, robenacoxib is cleared rapidly from the central body compartment but persists at sites of inflammation and tissue damage.[5,7]

The objective of the study reported here was to assess the efficacy and safety of robenacoxib for use in the management of perioperative pain and inflammation after orthopedic surgery in dogs. Because other NSAIDs are already registered in the European Union for this indication and are widely used, it was considered unethical to use a placebo. Therefore, meloxicam was selected as a positive control medication because it is widely used and is registered in the European Union for alleviation of inflammation and pain of acute and chronic musculoskeletal disorders in dogs (oral suspension) and for reduction of postoperative pain and inflammation following orthopedic and soft tissue surgery (injectable formulation). The efficacy of meloxicam for controlling pain associated with orthopedic surgery in dogs has been evaluated in several field studies.[8–12] The hypothesis for the study reported here was that robenacoxib would have efficacy and tolerability that did not differ significantly from those of meloxicam (statistical noninferiority hypothesis).

Materials and Methods

Animals—Dogs were selected from those admitted to 18 veterinary practices in France and 7 veterinary practices in Germany. All dogs were scheduled to undergo major orthopedic surgery. Because all dogs were client-owned animals, they were housed, managed, and fed as pets. Informed consent was obtained from owners of all dogs. The study was approved by the French and German regulatory authorities and Novartis committees after consideration of scientific, ethical, and animal welfare guidelines. The study was conducted in compliance with standards for good clinical practice[13] and published guidelines for studies conducted on efficacy of NSAIDs.[14] The report for the study was prepared by taking into account the CONSORT statement recommendations on reporting of noninferiority and equivalence randomized trials.[15]

Inclusion criteria for the study included dogs ≥ 6 weeks old (regardless of breed or sex) that weighed between 2.5 and 80 kg and were undergoing major orthopedic surgery. Exclusion criteria included dogs known to be pregnant or lactating, dogs with severe concomitant disorders of the kidneys, liver, or gastrointestinal tract that may have interfered with the evaluation of response to treatment, dogs that had received locally or systemically administered NSAIDs or opioids within 24 hours before inclusion in the study, or dogs that received corticosteroids within 30 days before inclusion in the study. In addition, once dogs were admitted to the study, they could be excluded if they had concomitant disorders (eg, trauma) that may have interfered with the evaluation of response to treatment, received a forbidden concomitant treatment (eg, rescue analgesia), or had adverse events that required cessation of treatment or if there was failure of compliance by the owner to administer drugs in accordance with the treatment protocol. Drugs likely to affect assessment of the main efficacy variables were disallowed; these drugs included analgesics (opioids and α_2-receptor agonists), other NSAIDs, corticosteroids, macrolides, and tetracyclines. All other concomitant treatments were recorded. Standard variables relating to anesthetic premedication, induction, maintenance, and recovery were recorded.

Study design—The study was a multicenter, prospective, parallel-group, randomized, blinded field study. Dogs were allocated into 2 treatment groups (robenacoxib and meloxicam) in a ratio of 2:1 (robenacoxib:meloxicam). Allocation to treatment groups was via a randomization list prepared by one of the authors (WS). No separate randomization was performed for age, body weight, or sex of dogs. Case allocation was stratified according to each attending veterinarian and the anticipated duration of surgery (which was dichotomized to ≤ 1 hour and > 1 hour). Maximum number of dogs assessed by any attending veterinarian was 12 for robenacoxib and 6 for meloxicam.

Because robenacoxib and meloxicam formulations differed, blinding was maintained via a double-investigator technique: the attending veterinarian was responsible for clinical assessments, whereas a second person (ie, the dispenser) was responsible for treatment prescription and drug administration. Four times during the study, the attending clinician accidentally gained knowledge of the treatment administered to a dog; each was during the final clinical examination of a dog. However, all dogs were included in the analysis because treatment was revealed to attending veterinarians after completion of the last clinical examination. Owners had knowledge of the treatments administered orally.

Two sets of numbered randomization envelopes (1 for surgeries with a predicted duration ≤ 1 hour and 1 for surgeries with a predicted duration > 1 hour) were prepared for each investigation center. After a dog was entered into the study by an attending veterinarian, the dispenser selected the envelope bearing the lowest number in the set corresponding to the anticipated duration of surgery and opened it to reveal the treatment allocation. Predicted durations were ≤ 1 hour for 38 dogs assigned to receive robenacoxib and 11 dogs assigned to receive meloxicam and > 1 hour for 59 dogs assigned to receive robenacoxib and 32 dogs assigned to receive meloxicam.

Treatments—Dogs in the robenacoxib group received an initial dose of robenacoxib[a] (2 mg/kg, SC) at the time of baseline assessment (prior to surgery) and then received additional doses of robenacoxib[b] (1 to 2 mg/kg, PO, q 24 h) beginning at 24 hours after extubation (day 1) and continuing for up to 15 days. The tablets contained 5 or 20 mg of robenacoxib/tablet and could not be divided to more closely approximate the correct dosage; tablets were administered with or without food.

Dogs in the meloxicam group received an initial dose of meloxicam[c] (0.2 mg/kg, SC) at the time of baseline assessment (prior to surgery) and then received additional doses of meloxicam[d] (0.1 mg/kg, PO, q 24 h) beginning on day 1 and continuing for up to 15 days. Meloxicam was mixed with food for oral administration.

Efficacy examinations and collection of samples—An efficacy examination was performed on all dogs before induction of anesthesia (baseline). Additional examinations were performed after surgery at 1, 2, 4, 8, and 24 hours after extubation (day 1) and at day 12.

Efficacy assessment—The primary end point for efficacy comprised the sum of scores for a Glasgow pain scale[16] (**Appendix**), which was assessed by a clinical investigator at each of 6 time points (1, 2, 4, 8, and 24 after extubation and 12 days after surgery [time of suture removal]). Maximum score for the Glasgow pain scale is 24; however, mobility (score B) could not be assessed in 29 dogs at early time points (total of 74 missing data points). Therefore, the primary end point of the study was a modified Glasgow score (maximum score, 20) that consisted of parts A, C, and D of the Glasgow pain scale but excluded part B.

Six secondary efficacy end points were assessed by clinical investigators and owners. Clinical investigators assessed pain in resting dogs by use of a VAS with a scale ranging from 0 (no pain) to 100 (severe pain manifested by vocalization, aggression, and refusal to allow examination) and also during gentle palpation or manipulation of the affected limb or joint by use of a VAS with a scale ranging from 0 (no pain elicited) to 100 (severe pain manifested by vocalization, aggression, and refusal to allow examination).[4] These VAS assessments were performed 7 times: at the time of administration of the robenacoxib or meloxicam prior to induction of anesthesia (baseline); at 1, 2, 4, 8, and 24 hours after extubation; and on day 12. Clinical investigators also made a global assessment of the efficacy (overall pain control) at 1 and 24 hours after extubation by use of a 4-point scale (0 = excellent, 1 = good, 2 = fair, and 3 = poor). Clinical investigators made an assessment of inflammation on day 12 on the basis of swelling of the affected joint or limb, local heat, redness, or paresis by use of a VAS with a scale ranging from 0 (no inflammation) to 100 (major inflammation).

Owners had knowledge of the treatments administered orally. Therefore, owner assessments of efficacy were secondary end points. Owners provided their perception of the severity of their dog's condition assessed daily from day 1 to day 12 by use of variables consistent with the Glasgow pain scales for demeanor (0 = normal, 1 = slightly modified, 2 = moderately modified, 3 = markedly modified, and 4 = severely modified) and mobility (0 = normal, 1 = slightly impaired, 2 = moderately impaired, 3 = markedly impaired, and 4 = severely impaired). Mobility could not be assessed in all dogs.

Plasma cortisol concentration—Venous blood samples were collected into tubes containing EDTA at baseline, extubation, and 1, 2, 4, and 8 hours after extubation and used for measurement of plasma cortisol concentrations. Plasma samples were stored at –20°C prior to analysis. Cortisol was measured by use of a commercial radioimmunoassay kit[e] by personnel at the National Veterinary School of Toulouse, France. Within-day and between-day precisions were < 14%, and the accuracy ranged from 93% to 109%. The limit of quantitation of the assay was 10 ng/mL.

Safety assessment—The safety of administered treatments was assessed on the basis of adverse events, local tolerance, results of hematologic and clinical biochemical analyses, and buccal mucosal bleeding time. An adverse event was defined as any observation that was unfavorable or unintended, regardless of whether it was considered to be a product-related event. Local tolerance was assessed by the dispenser as evidence of pain at the injection site at the time of the SC injection (baseline) on a scale ranging from 0 (no pain) to 3 (severe pain).

Venous blood samples (2 mL) were collected into tubes containing EDTA at baseline, day 1, and day 12 and used for measurement of hematologic variables (RBC counts, WBC counts, differential WBC counts, Hct, and hemoglobin concentration). Additional venous blood samples (5 mL) were collected at the same 3 times into serum tubes and used for measurement of serum activities of alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, and γ-glutamyltransferase and concentrations of total protein, urea, and creatinine.

Buccal mucosal bleeding times were measured at baseline and day 1.

Statistical analyses—Statistical tests were performed by use of commercially available software.[f] All evaluations were performed as 2-sided tests with significance set at 5%. The 95% CIs were calculated for the assessment of noninferiority. No correction for multiple tests was conducted because there was a single primary end point on which conclusions of efficacy were based, and the 6 secondary end points were used as supportive information only.

The experimental unit was each dog. All dogs that were allocated into 1 of the 2 groups were used for data analysis (intention-to-treat population), except for 1 dog that was excluded because no surgery was performed (pharyngitis did not allow intubation). As defined in the protocol, the primary analyses were conducted on the intention-to-treat population, and unless stated otherwise, results were for the intention-to-treat population.

Initial comparability tests

Demographic and baseline data were compared between groups by use of the Mann-Whitney *U* test for ordinal (eg, body weight and duration of surgery) or binary (eg, sex) data or the Kruskal-Wallis test for nonbinary nominal data (eg, combination of sex and neutered status).

Efficacy

Efficacy measures were averaged over time by use of a weighted mean corresponding to the area under the curve divided by time. The time range was 1 to 24 hours for Glasgow scores (or 2 or 4 to 24 hours when a dog recovered consciousness more than 1 hour after extubation) or day 1 to day 12 for owner assessments. For global efficacy and inflammation scores, time averaging was not performed because there was only 1 measurement for each. Missing values were imputed by use of the last-observation-carried-forward meth-

od. Efficacy measures for each response were logarithmically transformed and then analyzed by use of an ANOVA.

Noninferiority

Noninferiority was defined on a relative scale. The quotient for the 95% CI of the efficacy of robenacoxib divided by the 95% CI of the efficacy of meloxicam should completely lie above a predefined threshold of $1 - \sigma$. The value of $\sigma = 0.20$ was selected to account for minimum clinically relevant differences and anticipated moderate to high between-dog variability. Reciprocal pain scores were used as an efficacy measure; thus, the lower limit of the 95% CI for (1/mean score robenacoxib)/(1/mean score meloxicam) should be > 0.80.

Hematologic and clinical biochemical results and bleeding time

Because normality of these data was uncertain, nonparametric methods were applied. The Mann-Whitney *U* test was used to compare the 2 groups. Data were compared for before surgery, for after surgery, and for the change between before and after surgery. In addition, data after surgery were compared with data before surgery for each group by use of the Wilcoxon paired-samples test.

Adverse effects

The incidence of adverse events in the 2 groups was compared with the Fisher exact probability test.

Sample size and statistical unit

The experimental unit was each dog. The study was planned to include a minimum of 150 dogs (100 receiving robenacoxib and 50 receiving meloxicam). The sample size was calculated for 80% power in the noninferiority analysis as determined for results obtained by use of the Glasgow scale, allowing for the relatively large SDs obtained in a preliminary study conducted by one of the authors (PG; data on file). Recruitment was terminated at 141 dogs, and this number proved sufficient to achieve the objectives of the study.

Results

Baseline data and dosages administered—A total of 141 dogs were included in the study. One dog was removed because it did not undergo surgery (pharyngitis prevented intubation); thus, 140 dogs (97 received robenacoxib and 43 received meloxicam) were used for the intention-to-treat analysis. Of the 140 dogs, 136 were in the per-protocol population because 4 dogs had major deviations from the protocol (postinclusion removal because of forbidden concomitant treatment [n = 3 dogs] and an adverse event unrelated to treatment [ie, trauma;1 dog]). Data for these dogs were included in intention-to-treat analyses, although a separate per-protocol analysis was also performed for the primary end point.

Results for demographic and baseline variables plus types of orthopedic surgery were calculated (**Table 1**). There were no significant differences between the 2 groups at baseline, except for the frequency of surgery

Table 1—Demographic variables at baseline for dogs receiving robenacoxib or meloxicam and undergoing orthopedic surgery.

Variable	Robenacoxib	Meloxicam	Both treatments	*P* value*
No. of dogs	97	43	140	NA
Age (y)†	4.2 ± 3.7	3.5 ± 3.1	4.0 ± 3.5	0.26
Body weight (kg)†	24.5 ± 13.5	24.3 ± 16.2	24.5 ± 14.3	0.60
Sex and neutered status‡				
Male not neutered	45 (46)	21 (49)	66 (47)	0.95
Female not neutered	29 (30)	11 (26)	40 (29)	0.95
Male neutered	5 (5)	2 (5)	7 (5)	0.95
Female neutered	18 (19)	9 (21)	27 (19)	0.95
Surgery during the preceding 6 months	14	1	15	0.04
Pain before surgery (VAS score)				
At rest†	19.9 ± 20.2	23.4 ± 22.6	21.0 ± 20.9	0.39
During palpation or manipulation†	43.3 ± 28.0	50.1 ± 28.5	45.4 ± 28.3	0.21
Type of surgery§				
Ruptured cruciate ligament	35	9	44	0.08
Femoral head and neck excision	13	4	17	0.58
Elbow joint arthrotomy	5	3	8	0.70
Osteochondrosis dissecans	5	3	8	0.70
Fracture	25	10	35	0.83
Other orthopedic surgery	17	15	32	0.03
Duration of surgery (h)†	1.25 ± 0.74	1.31 ± 0.58	1.27 ± 0.70	0.22
Duration of intubation (h)†	2.06 ± 1.02	2.19 ± 0.89	2.10 ± 0.98	0.37
Interval between injection of robenacoxib or meloxicam and extubation (h)†	2.31 ± 1.01	2.43 ± 0.90	2.34 ± 0.97	0.37
Duration of oral administration (d)†	11.5 ± 2.7	11.3 ± 1.8	11.5 ± 2.5	0.10

Each dog in its respective treatment group received an initial dose (2 mg of robenacoxib/kg or 0.2 mg of meloxicam/kg, SC) before surgery and daily doses (1 to 2 mg of robenacoxib/kg or 0.1 mg of meloxicam/kg, PO) for up to 15 days after surgery.

*Values were considered significant at $P < 0.05$ (Fisher exact probability test). †Value reported is mean ± SD. ‡Value reported is number (percentage); values in a column may not sum to 100% because of rounding. §Values are numbers of dogs; some dogs underwent 2 surgeries during the same anesthetic event.

NA = Not applicable.

Table 2—Results of ANOVA estimates for group means and pairwise group comparisons of dogs receiving robenacoxib or meloxicam and undergoing orthopedic surgery.

Variable	Group	Estimate	SE	95%CI
Primary end point*				
Sum of modified Glasgow scale	Robenacoxib	1.91	0.14	1.65–2.19
	Meloxicam	2.37	0.24	1.93–2.88
Sum of entire Glasgow scale	Robenacoxib	3.75	0.24	3.30–4.26
	Meloxicam	4.07	0.34	3.44–4.79
Secondary end points				
Pain at rest†	Robenacoxib	6.51	0.75	5.16–8.15
	Meloxicam	5.85	0.93	4.24–7.95
Pain during palpation or manipulation†	Robenacoxib	14.67	1.58	11.85–18.12
	Meloxicam	15.22	2.19	11.41–20.20
Clinical investigator assessment of global efficacy‡	Robenacoxib	0.62	0.06	0.50–0.75
	Meloxicam	0.67	0.10	0.49–0.87
Clinical investigator assessment of global inflammation score†	Robenacoxib	1.92	0.47	1.13–3.01
	Meloxicam	1.83	0.63	0.83–3.40
Owner assessment of demeanor§	Robenacoxib	0.23	0.03	0.17–0.29
	Meloxicam	0.27	0.05	0.18–0.36
Owner assessment of mobility§	Robenacoxib	0.87	0.06	0.76–1.00
	Meloxicam	0.78	0.09	0.62–0.96

*The modified Glasgow scale excluded the assessment of mobility and the maximum score is 20, whereas the maximum score for the entire Glasgow scale is 24. †Maximum score is 100 (VAS). ‡Maximum score is 3 (NRS). §Maximum score is 4 (NRS).
See Table 1 for remainder of key.

during the preceding 6 months and the frequency of surgeries categorized as other. Baseline (prior to anesthesia) pain score did not differ significantly between the groups, either when dogs were at rest ($P = 0.39$) or during palpation or manipulation of the affected joint or limb ($P = 0.21$). The duration of surgery (mean, 1.27 hours) and intubation (mean, 2.1 hours) did not differ significantly between groups. The most frequent types of surgery were performed for repair of ruptured cruciate ligaments (44/140 [31%]) and fractures (35/140 [25%]).

The targeted dosage of robenacoxib for SC administration was 2.00 mg/kg. Actual mean dosage administered was 2.01 mg/kg (minimum, 1.68 mg/kg; maximum, 2.29 mg/kg). The targeted dosage of meloxicam for SC administration was 0.20 mg/kg; actual mean dosage administered was 0.22 mg/kg (minimum, 0.17 mg/kg; maximum, 0.50 mg/kg).

The targeted dosage of robenacoxib for oral administration was 1 to 2 mg/kg administered once daily. Because the tablets could not be divided, actual dosages varied. The mean dosage administered orally was 1.40 mg/kg (median, 1.36 mg/kg; minimum, 0.98 mg/kg; and maximum, 1.98 mg/kg). The tablets were administered with or without food, as determined by each owner, for up to 15 days (mean ± SD, 11.5 ± 2.7 days; median, 12 days). Eighty-eight of 97 (91%) dogs received orally administered doses for ≥ 10 days. In the remaining 9 (9%) dogs, the shorter duration of treatment was attributable to owner error or withdrawal of the dog from the study. For the 97 dogs, robenacoxib tablets were administered in the food (21 [22%] dogs), with a small quantity of food (42 [43%] dogs), directly in the mouth other than at feeding time (31 [32%] dogs), or not specified (3 [3%] dogs).

The targeted dosage of meloxicam for oral administration was 0.1 mg/kg. Meloxicam was administered (in accordance with the manufacturer's instructions) mixed with food for up to 15 days (mean, 11.3 ± 1.8 days; median, 11 days). Mean dosage orally administered was 0.10 mg/kg (median, 0.10 mg/kg; minimum, 0.09 mg/kg; and maximum, 0.15 mg/kg). Forty of 43 (93%) dogs were orally administered meloxicam for ≥ 10 days. In the other 3 (7%) dogs, the shorter duration of administration was attributable to owner errors or withdrawal of the dog from the study.

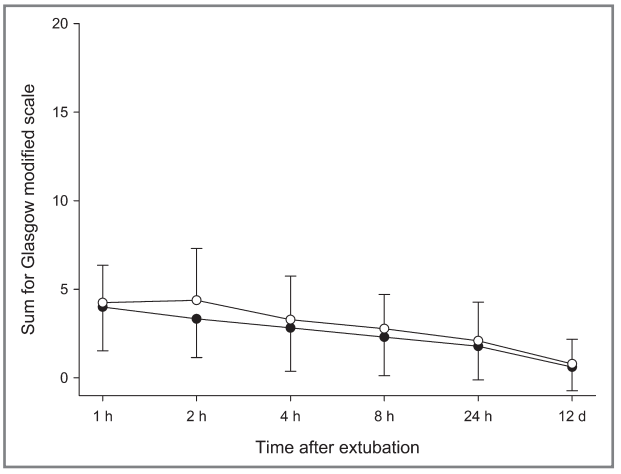

Figure 1—Mean ± SD scores for a modified Glasgow pain scale (ie, without the score for mobility) assessed by clinical investigators as the primary end point for dogs treated with robenacoxib (n = 97 [black circles]) or meloxicam (43 [white circles]) to alleviate pain associated with orthopedic surgery. Each dog in its respective treatment group received an initial dose (2 mg of robenacoxib/kg or 0.2 mg of meloxicam/kg, SC) before surgery and daily doses (1 to 2 mg of robenacoxib/kg or 0.1 mg of meloxicam/kg, PO) for up to 15 days after surgery. The score represents an NRS ranging from 0 to 20.

For both treatment groups, dosing compliance was monitored by the dispenser. Owners were required to complete and return accounting forms and to return all unused products and empty packets.

Rescue treatment and concomitant treatments— Attending clinicians were authorized to provide rescue treatment during the first 24 hours after surgery. However, no dogs required such treatment.

Attending clinicians were advised to avoid concomitant treatment, if possible. Concomitant treatments included drugs used for anesthesia that were permitted in the study protocol. Premedicants administered included no drugs (n = 33 dogs), acepromazine (70), diazepam (34), glycopyrollate (4), and atropine (1). Opioids and α_2-receptor agonists were not allowed as premedicants. Anesthesia was induced with thiopentone (n = 115 dogs) or propofol (25) and maintained with halothane (79) or isoflurane (61). There were no significant (P = 0.94) differences between the 2 groups with regard to the drugs used and no significant (P = 0.37) difference in the amount of time that elapsed between SC administration of meloxicam or robenacoxib and extubation.

Additional allowed concomitant treatments were primarily fluids (n = 122 dogs) and antimicrobials administered via injection (121) or orally (111). There were no significant differences between the groups with regard to distribution of these treatments.

Three dogs (all in the robenacoxib group) were administered 4 disallowed drugs (dexamethasone, morphine, ketamine, and meloxicam). All drugs were administered as single doses. Data from these dogs were retained in the intention-to-treat analysis but were not included in the per-protocol analysis.

Efficacy—The primary end point defined in the study protocol was the arithmetic sum of the 6 scores assigned by a clinical investigator for the Glasgow scale at 1, 2, 4, 8, and 24 hours after extubation and at day 12. The maximum possible score was 24. However, the protocol provided for the possibility that the mobility score would not be assessed if locomotion was not possible at the time of assessment. Thus, mobility was not assessed in 29 dogs (maximum possible score for these dogs was 20). Because it is not valid to compare dogs for which data with mobility were scored or were not scored, it was decided that the main primary end point for the study would be the modified Glasgow score without the mobility assessment. However, similar results were obtained for assessments performed with the entire Glasgow scale and with the modified Glasgow scale with mobility omitted (**Table 2**).

The fact that pain was well controlled in the immediate postoperative period by both robenacoxib and meloxicam was indicated by mean scores for the Glasgow pain scale of < 5 (111 dogs with mobility assessment excluded; maximum score = 20; **Figure 1**) and < 7 (140 dogs with mobility assessment included; maximum score = 24) at 1 and 2 hours after extubation. Thereafter, scores decreased steadily, and mean values for both groups were < 1 (111 dogs with mobility assessment excluded) and < 2 (140 dogs with mobility assessment included) by day 12.

The ANOVA estimates for differences in overall group means and pairwise group mean values were determined (Table 2). For both primary and secondary efficacy variables, mean values were similar between the groups and there were no significant differences.

A noninferiority analysis was performed (**Table 3**). Noninferiority of robenacoxib relative to meloxicam was indicated by CI values > 0.80 for the primary end point (ie, the sum of Glasgow pain scale scores with or without mobility assessment). In addition to the main intention-to-treat analysis for 140 dogs, noninferiority analysis was repeated on the per-protocol population of 136 dogs. Similar results were obtained with both analyses. For the primary end point of the per-protocol population, the reciprocal of the scores for the robenacoxib-to-meloxicam ratio was 1.12 (95% CI, 0.97 to 1.30), whereas it was 1.16 (95% CI, 0.98 to 1.37) for the intention-to-treat population. Therefore, there was noninferiority for both populations.

Plasma cortisol concentration—Plasma cortisol concentrations were measured in samples obtained at baseline and up to 8 hours after extubation (**Table 4**). Significant (P < 0.001) and quantitatively similar increases were obtained for both groups, when compared with preanesthesia values. However, concentrations in both groups were similar to the preanesthesia values by 4 hours after extubation. Comparison of the groups by use of an ANOVA indicated no significant (P = 0.31)

Table 3—Results of ANOVA estimates for group quotients of the robenacoxib-to-meloxicam ratio and noninferiority analysis of the efficacy of robenacoxib, compared with the efficacy of meloxicam, for dogs receiving robenacoxib or meloxicam and undergoing orthopedic surgery.

Variable	Estimate	SE	95% CI	*P* value
Primary end point*				
1/sum of modified Glasgow scale	1.16	0.10	0.98–1.37†	0.09
1/sum of entire Glasgow scale	1.07	0.08	0.92–1.24†	0.38
Secondary end points				
1/pain at rest	0.91	0.13	0.69–1.21	0.52
1/pain during palpation or manipulation	1.04	0.15	0.78–1.37	0.81
1/clinical investigator assessment of global efficacy score	1.03	0.07	0.90–1.18†	0.67
1/clinical investigator assessment of global inflammation score	0.97	0.22	0.62–1.51	0.89
1/owner assessment of demeanor	1.03	0.05	0.95–1.13†	0.47
1/owner assessment of mobility	0.95	0.06	0.85–1.07†	0.40

Values reported are reciprocals of scores; thus, values > 1.00 indicate lower scores (higher efficacy) for robenacoxib, compared with scores for meloxicam.

†For values with a lower limit of the 95% CI > 0.80, noninferiority of robenacoxib (compared with meloxicam) was concluded.

See Tables 1 and 2 for remainder of key.

differences between the robenacoxib and meloxicam groups.

Safety—The frequency of dogs with recorded adverse events did not differ significantly ($P = 0.45$) between groups (robenacoxib, 24/97; meloxicam, 10/43). Most adverse events were classified as benign. Most reports concerned the gastrointestinal tract (vomiting, diarrhea, dark feces, or soft feces). A single life-threatening event (lymphangiectasia and edema of the hind limbs of a dog following surgery to remove cement from a hip joint prosthesis) was classified as unrelated to treatment.

Pain at the site of SC injections was minimal. It was reported as absent in 92 dogs, slight in 4 dogs, and was not assessed in 1 dog (robenacoxib group) and was absent in 40 dogs and slight in 3 dogs (meloxicam group). Mean ± SD scores for pain at injection sites were 0.04 ± 0.20 for robenacoxib and 0.07 ± 0.26 for meloxicam and did not differ significantly ($P = 0.68$) between groups.

Mean ± SD buccal mucosal bleeding time after administration of robenacoxib was not significantly ($P = 0.78$) different at 24 hours after extubation (137 ± 48 seconds), compared with the value before surgery (138 ± 55 seconds). For meloxicam, bleeding times also did not differ significantly ($P = 0.057$) between values obtained before surgery (131 ± 51 seconds) and 24 hours after extubation (117 ± 45 seconds).

Analysis of hematologic and clinical biochemical data revealed no changes that were regarded as biologically relevant. However, there were several variables whose values differed significantly from the baseline values, and these generally were detected in both treatment groups. The RBC count, Hct, and γ-glutamyltransferase activity decreased in both groups at 1 and 24 hours after extubation. The hemoglobin concentration decreased in the robenacoxib group at 1 and 24 hours after extubation. Numbers of eosinophils and platelets increased in both groups at day 12. The WBC count and number of neutrophils increased at 1 and 24 hours after extubation in both groups and at day 12 in the meloxicam group. Numbers of lymphocytes and monocytes and the alkaline phosphatase activity increased at 1 and 24 hours after extubation and at day 12 in both groups. The alanine aminotransferase activity decreased in the robenacoxib group at day 12, whereas the aspartate aminotransferase activity increased at 1 and 24 hours after extubation in both groups and decreased at day 12 in the robenacoxib group. Total protein concentration decreased at 1 hour after extubation and at day 12 in both groups. Urea concentration decreased at 1 and 24 hours after extubation in both groups and increased at day 12 in the meloxicam group. Finally, the creatinine concentration decreased at 1 and 24 hours after extubation in both groups and increased at day 12 in the robenacoxib group.

Table 4—Mean ± SD plasma cortisol concentration (ng/mL) at various time points before and after orthopedic surgery in 97 dogs receiving robenacoxib and 43 dogs receiving meloxicam.

	Robenacoxib		Meloxicam	
Time	n	Mean	n	Mean
Baseline*	91	73.03 ± 41.99	41	76.85 ± 41.36
Extubation	92	159.70 ± 61.16	41	156.07 ± 81.14
1 hour after extubation	92	162.35 ± 86.78	41	161.29 ± 67.31
2 hours after extubation	92	130.53 ± 77.65	41	133.24 ± 63.74
4 hours after extubation	92	84.52 ± 43.94	41	81.59 ± 33.92
8 hours after extubation	92	76.84 ± 33.94	41	64.98 ± 25.56
Mean	92	105.65 ± 46.85	41	101.74 ± 35.68

*Represents the time at which robenacoxib or meloxicam was administered prior to induction of anesthesia on the day of surgery.
n = Number of dogs.
See Table 1 for remainder of key.

Discussion

The principal finding of the study reported here was that a treatment regimen consisting of a single SC injection of robenacoxib before surgery followed by once-daily oral administration of robenacoxib tablets for up to 15 days had similar efficacy and tolerability for the management of pain and inflammation associated with orthopedic surgery when compared with results for a positive control treatment (ie, meloxicam injection followed by oral administration of meloxicam). Both robenacoxib and meloxicam provided good efficacy, which was evident from the lack of rescue treatments required for any dog and the low scores for pain and inflammation at all time points after surgery. Therefore, the results are clinically relevant and provide statistical proof of the similarity of effect.

A major strength of this study was that it was designed as a multicenter, prospective, randomized, parallel-group, blinded field trial. The study had adequate power because the similarity of robenacoxib and the positive control treatment was proven statistically for the primary end point. Three major factors contributed to the power in the study. First, the mean efficacy of robenacoxib was numerically higher than for meloxicam (1.16 for the ratio of the reciprocals of the primary end point). Second, there was moderate variability (SEs were < 10% of the mean) for the primary end point. Third, there were few serious protocol deviations that resulted in premature withdrawal of dogs from the study.

It can be difficult to clinically assess pain in animals. In the study reported here, the primary end point was a clinical investigator's assessment of pain by use of a Glasgow pain scale for 6 separate indices. At the time of the study, the weight for the factors to be applied to the components of the scale had not yet been published[1,17]; thus, each variable of the scale was assessed as an NRS. This assessment was supported by 6 secondary end points (evaluation of pain at rest, pain during palpation or manipulation, and inflammation assessed by a clinical investigator via a VAS; a global assessment of efficacy conducted by a clinical investigator via an NRS; and the owner's evaluation of demeanor and mobility over the duration of the study).

The study did have limitations. First, the number of dogs included (97 for robenacoxib and 43 for meloxicam) was not perfectly balanced in accordance with the ratio of 2:1 planned in the study design. This was the result of the fact that 10 veterinarians each recruited < 4 dogs for the study and 6 veterinarians each recruited only a single dog for the study. Because the protocol did not define a minimum number of dogs per site, all dogs were included in the analysis.

Second, although the dogs were assessed fairly intensively by a veterinarian during the first 24 hours after surgery, follow-up assessments (from day 2 until the final visit to a veterinarian) were less intensive and relied on each owner's daily assessments of their dog's demeanor and mobility. This technique was used because it was judged unacceptable to hospitalize the dogs unnecessarily beyond 24 hours after surgery or to require extra visits to a veterinarian.

Third, although the assessments made by the veterinarians were conducted in a blinded manner via the use of a dispenser to manage the test treatments, dog owners were aware of the treatment. Therefore, the primary end point of the study was based on assessments performed by a veterinarian and not on assessments performed by the owners.

Finally, the limitations of noninferiority studies that involve use of positive control treatments have been established.[15] In the study reported here, use of a placebo would have been unethical because a number of NSAIDs are registered in the European Union for perioperative use in dogs and are widely used. Meloxicam was selected as the positive control treatment because it is used extensively in dogs and has proven efficacy for alleviation of perioperative pain and inflammation.

The efficacy of meloxicam in the management of pain and inflammation associated with orthopedic surgery in dogs has been evaluated in several studies. A single dose of meloxicam (0.2 mg/kg, IV) administered in combination with butorphanol prior to surgery resulted in significantly lower scores for an adjusted pain score at some time points, compared with the effects for butorphanol alone, in 40 dogs undergoing cruciate surgery.[8] In another field study,[10] there was slight but not significant efficacy for meloxicam versus a negative control treatment in 20 dogs undergoing cruciate repair and epidural anesthesia. In 3 additional field studies,[9,11,12] meloxicam was reported to have efficacy equivalent to that of carprofen, fentanyl, and ketoprofen. In addition, the efficacy of meloxicam at the dosages used in the present study has been established, compared with results for a placebo, in animals with experimentally induced urate synovitis. Administration of 0.2 mg of meloxicam/kg via SC injection[18] and repeated oral administration of 0.1 mg of meloxicam/kg[19] had significantly better efficacy, compared with results for a placebo. Therefore, we conclude that there is satisfactory evidence for the efficacy of meloxicam in control of pain and inflammation in dogs undergoing orthopedic surgery. However, the Glasgow pain scale was not used in any of these aforementioned studies. In optimally designed noninferiority studies, the methods and outcome measures should be similar to those used in the original evaluation of the active control product.[15]

We are not aware of any published data on the efficacy of orally administered meloxicam for the treatment of postoperative pain and inflammation for up to 15 days, as was used in the present study. Although the pain associated with osteoarthritis in dogs may differ in character and intensity from that after orthopedic surgery, it was found in a meta-analysis of 16 clinical trials that only for meloxicam did a high degree of comfort exist in relation to efficacy for the treatment of osteoarthritis in dogs.[20] As mentioned previously, oral administration of meloxicam at a dosage of 0.1 mg/kg had significant efficacy in animals with experimentally induced urate synovitis.[19] Therefore, there is sufficient evidence for the efficacy of meloxicam to justify its use as the positive control treatment in the study reported here. The safety of meloxicam for use during surgery in dogs has also been evaluated, with no reported adverse effects on the cardiovascular system and kidneys.[21–23]

An additional limitation of the noninferiority design of the present study was the choice of a noninferiority threshold (ie, δ) value of 0.20, the same value recommended in guidelines for bioequivalence studies. Noninferiority margins should be the largest margin that can be clinically acceptable; to our knowledge, specific recommendations for noninferiority margins for veterinary NSAIDs have not been published. In fact, the results indicated that efficacy of robenacoxib similar to that of the positive control treatment would also have been achieved if we had defined a value of $\delta = 0.05$ for the primary end point (ie, a maximum difference of 5% for modified Glasgow pain scores).

Clinical investigators were instructed to provide rescue treatment if they judged it to be necessary. None of the dogs required rescue treatment, which may indicate that the measurements were insensitive. However, the low scores for pain at all times after surgery support an alternative conclusion that both treatment regimens were effective in preventing most of the perioperative pain and inflammation so that additional treatment was not necessary.

Plasma cortisol concentrations at the time of extubation in both groups were twice as high as the preanesthesia values. However, the increase was transient, and concentrations returned to baseline values by 4 hours after extubation. The extent and duration of the observed increase in cortisol concentrations are consistent with results of other studies[24–26] in which investigators reported increases in concentrations (by a factor of 2 to 3) that lasted 2 to 4 hours. In addition to anesthesia, the stress of surgery (especially major surgical intervention involved in most orthopedic cases), with associated cardiovascular and body fluid changes, may also increase circulating cortisol concentrations. In these clinical cases, the mean duration of surgery was 75 minutes. There were no significant differences between the treatment groups with regard to cortisol concentrations. In another study,[8] significantly lower plasma cortisol concentrations were detected in dogs undergoing cruciate repair and receiving meloxicam than in dogs that did not receive an NSAID. However, no changes in plasma cortisol concentrations were detected after meloxicam administration in dogs undergoing mammary gland excision in yet another study.[23]

Hematologic and clinical biochemical data, results of examinations by the clinical investigators, and reported adverse events indicated that both NSAIDs investigated in the present study were tolerated well. Although a range of adverse effects were reported, these were all assessed as mild or benign (except for 1 adverse effect that was not a treatment-related event), and most were judged to be not related to treatment or only questionably related to treatment. The most frequently reported adverse effects involved the gastrointestinal

system. Such adverse effects as occasional vomiting and loose feces are commonly reported in trials of this kind, including those that have incorporated a placebo treatment.

No change in buccal mucosal bleeding time before and after surgery was observed with robenacoxib. This is not surprising because robenacoxib used at recommended dosages does not inhibit COX-1 in dogs.[6,18] Robenacoxib used at elevated dosages in safety studies did not affect buccal bleeding time or hematologic results.[27] Buccal bleeding time also did not increase with meloxicam treatment, as reported previously in dogs undergoing abdominal or orthopedic surgery.[3,28,29]

We concluded that a treatment regimen consisting of a single SC injection of robenacoxib (2 mg/kg) before surgery followed by once-daily oral administration (1 to 2 mg/kg) of tablets after surgery for 10 to 15 days had similar efficacy and tolerability, compared with results for meloxicam, for the control of pain and inflammation in dogs undergoing orthopedic surgery.

a. Onsior injection, 20 mg/mL, Novartis Santé Animale, Huningue, France.
b. Onsior tablets, Novartis Santé Animale, Huningue, France.
c. Metacam, 5 mg/mL solution for injection, Labiana Life/Sciences SA, Terrassa, Spain.
d. Metacam oral suspension, Boehringer Ingelheim Pharma GmbH & Co KG, Ingelheim am Rhein, Germany.
e. IM-1841, Immunotech, Marseille, France.
f. SAS, version 8.2, SAS Institute Inc, Cary, NC.

References

1. AAHA/AAFP Pain Management Guidelines Task Force. AAHA/AAFP pain management guidelines for dogs and cats. *J Feline Med Surg* 2007;9:466–480.
2. Morton CM, Reid J, Scott EM, et al. Application of a scaling model to establish and validate an interval level pain scale for assessment of acute pain in dogs. *Am J Vet Res* 2005;66:2154–2166.
3. Mathews KA, Pettifer G, Foster R, et al. Safety and efficacy of preoperative administration of meloxicam, compared with that of ketoprofen and butorphanol in dogs undergoing abdominal surgery. *Am J Vet Res* 2001;62:882–888.
4. Reid J, Nolan AM. A comparison of the postoperative analgesic and sedative effects of flunixin and papaveretum in the dog. *J Small Anim Pract* 1991;32:603–608.
5. King JN, Dawson J, Esser RE, et al. Preclinical pharmacology of robenacoxib: a novel selective inhibitor of cyclooxygenase-2. *J Vet Pharmacol Ther* 2009;32:1–17.
6. King JN, Rudaz C, Borer L, et al. In vitro and ex vivo inhibition of canine cyclooxygenase isoforms by robenacoxib: a comparative study. *Res Vet Sci* 2010;88:497–506.
7. Brune K, Furst DE. Combining enzyme specificity and tissue selectivity of cyclooxygenase inhibitors: towards better tolerability? *Rheumatology (Oxford)* 2007;46:911–919.
8. Budsberg SC, Cross AR, Quandt JE, et al. Evaluation of intravenous administration of meloxicam for perioperative pain management following stifle joint surgery in dogs. *Am J Vet Res* 2002;63:1557–1563.
9. Deneuche AJ, Dufayet C, Goby L, et al. Analgesic comparison of meloxicam or ketoprofen for orthopedic surgery in dogs. *Vet Surg* 2004;33:650–660.
10. Fowler D, Isakow K, Caulkett N, et al. An evaluation of the analgesic effects of meloxicam in addition to epidural morphine/mepivacaine in dogs undergoing cranial cruciate ligament repair. *Can Vet J* 2003;44:643–648.
11. Lafuente MP, Franch J, Durall I, et al. Comparison between meloxicam and transdermally administered fentanyl for treatment of postoperative pain in dogs undergoing osteotomy of the tibia and fibula and placement of a uniplanar external distraction device. *J Am Vet Med Assoc* 2005;227:1768–1774.
12. Laredo FG, Belda E, Murciano J, et al. Comparison of the analgesic effects of meloxicam and carprofen administered preoperatively to dogs undergoing orthopaedic surgery. *Vet Rec* 2004;155:667–671.
13. VICH Steering Committee. Guideline for good clinical practice (VICH GL9, EMEA/CVMP/VICH/595/98, 2000). Available at: www.ema.europa.eu. Accessed Oct 18, 2010.
14. CVMP. Guideline for the conduct of efficacy studies for non-steroidal anti-inflammatory drugs (EMEA/CVMP/237/01, 2001). Available at: www.ema.europa.eu. Accessed Oct 18, 2010.
15. Piaggio G, Elbourne DR, Altman DG, et al. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. *JAMA* 2006;295:1152–1160.
16. Holton L, Reid J, Scott EM, et al. Development of a behaviour-based scale to measure acute pain in dogs. *Vet Rec* 2001;148:525–531.
17. Murrell JC, Psatha EP, Scott EM, et al. Application of a modified form of the Glasgow pain scale in a veterinary teaching centre in the Netherlands. *Vet Rec* 2008;162:403–408.
18. Schmid VB, Spreng DE, Seewald W, et al. Analgesic and anti-inflammatory actions of robenacoxib in acute joint inflammation in the dog. *J Vet Pharmacol Ther* 2010;33:118–131.
19. Cross AR, Budsberg SC, Keefe TJ. Kinetic gait analysis assessment of meloxicam efficacy in a sodium urate-induced synovitis model in dogs. *Am J Vet Res* 1997;58:626–631.
20. Aragon CL, Hofmeister EH, Budsberg SC. Systematic review of clinical trials of treatments for osteoarthritis in dogs. *J Am Vet Med Assoc* 2007;230:514–521.
21. Bostrom IM, Nyman G, Hoppe A, et al. Effects of meloxicam on renal function in dogs with hypotension during anaesthesia. *Vet Anaesth Analg* 2006;33:62–69.
22. Crandell DE, Mathews KA, Dyson DH. Effect of meloxicam and carprofen on renal function when administered to healthy dogs prior to anesthesia and painful stimulation. *Am J Vet Res* 2004;65:1384–1390.
23. Nakagawa K, Miyagawa Y, Takemura N, et al. Influence of preemptive analgesia with meloxicam before resection of the unilateral mammary gland on postoperative cardiovascular parameters in dogs. *J Vet Med Sci* 2007;69:939–944.
24. Egger CM, Glerum L, Michelle HK, et al. Efficacy and cost-effectiveness of transdermal fentanyl patches for the relief of post-operative pain in dogs after anterior cruciate ligament and pelvic limb repair. *Vet Anaesth Analg* 2007;34:200–208.
25. Kona-Boun JJ, Cuvelliez S, Troncy E. Evaluation of epidural administration of morphine or morphine and bupivacaine for postoperative analgesia after premedication with an opioid analgesic and orthopedic surgery in dogs (Erratum published in *J Am Vet Med Assoc* 2006;229:1755). *J Am Vet Med Assoc* 2006;229:1103–1112.
26. Sibanda S, Hughes JM, Pawson PE, et al. The effects of preoperative extradural bupivacaine and morphine on the stress response in dogs undergoing femoro-tibial joint surgery. *Vet Anaesth Analg* 2006;33:246–257.
27. King JN, Arnaud JP, Goldenthal EI, et al. Robenacoxib in the dog: target species safety in relation to extent and duration of inhibition of COX-1 and COX-2 [published online ahead of print Jul 14, 2010]. *J Vet Pharmacol Ther* doi:10.1111/j.1365-2885.2010.01209.x.
28. Fresno L, Moll J, Penalba B, et al. Effects of preoperative administration of meloxicam on whole blood platelet aggregation, buccal mucosal bleeding time, and haematological indices in dogs undergoing elective ovariohysterectomy. *Vet J* 2005;170:138–140.
29. Kazakos GM, Papazoglou LG, Rallis T, et al. Effects of meloxicam on the haemostatic profile of dogs undergoing orthopaedic surgery. *Vet Rec* 2005;157:444–446.

Appendix appears on the next page

Appendix

Glasgow pain scale used by clinical investigators as the primary end point for the assessment of pain in dogs after orthopedic surgery.

Part	Variable	Score and description
A1	Vocalization*	0 Dog is quiet 1 Dog cries or whimpers 2 Dog groans 3 Dog screams
A2	Attention to wound area*	0 Dog ignores wound or area 1 Dog looks at wound or area 2 Dog licks wound or area 3 Dog rubs wound or area 4 Dog chews wound or area
B	Mobility†	0 Dog stands and walks normally 1 Dog is lame 2 Dog is slow or reluctant to move 3 Dog is stiff 4 Dog refuses to move
C	Response to touch	0 Dog does not respond 1 Dog looks around 2 Dog flinches 3 Dog growls or guards area 4 Dog attempts to bite 5 Dog cries
D1	Demeanor	0 Dog is happy and content or happy and bouncy 1 Dog is quiet 2 Dog is indifferent or nonresponsive to surroundings 3 Dog is nervous, anxious, or fearful 4 Dog is lethargic or nonresponsive to stimulation
D2	Posture	0 Dog is comfortable 1 Dog is unsettled 2 Dog is restless 3 Dog is hunched or tense 4 Dog is rigid

All parts were assessed sequentially at 6 examination times after extubation (at 1, 2, 4, 8, and 24 hours and day 12). Mobility (part B) could not be assessed in 29 dogs at early time points after extubation; therefore, the main end point of the study was the score for a modified Glasgow scale based on parts A, C, and D (ie, maximum of 20 points).

*Dog was in a kennel during this assessment. †Dog was out of kennel on a lead during this assessment.