Evaluation of Gabapentin in the Treatment of Postoperative Pain after a Tibial Plateau Levelling Osteotomy in Dogs

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Abstract

Objective Pain management is an essential component of perioperative patient care. Multimodal pain management strategies have the potential to provide more effective analgesia than a single drug. The objective of this study was to evaluate the use of gabapentin as an adjuvant to carprofen for the management of postoperative pain following tibial plateau levelling osteotomy surgery.

Materials and Methods The study included 20 adult dogs with unilateral cranial cruciate ligament disease, assigned to one of two postoperative treatment groups, receiving either carprofen (4.4 mg/kg orally every 24 hours) or carprofen plus gabapentin 20 mg/kg, orally, every 8 hours beginning the night prior to surgery and continuing for 14 days postoperatively. The patients were blindly assessed postoperatively using the Short Form of the Glasgow Composite Measure Pain Scale (GCMPS-SF) and limb function measured by pressure platform gait analysis. There was no difference in body weight, age, affected hindlimb or sex between groups.

Result No differences were found in (GCMPS-SF) pain assessments; after surgery, a (GCMPS-SF) more than or equal to 6 was documented in four dogs (two dogs in each group) and no dog required rescue analgesia more than once.

Conclusion In this population of dogs, the addition of oral gabapentin at the dose and frequency studied did not improve subjective or objective outcome measures for perioperative pain control following tibial plateau levelling osteotomy surgery.

Keywords
- analgesia
- gabapentin
- TPLO
- dogs

Introduction

Treatment of perioperative pain in veterinary surgical patients is a cornerstone of modern anaesthetic practice. Perioperative pain management has a direct impact on patient well-being and the prevention of the development of chronic and maladaptive pain states.[1]

Acute postoperative pain, in its sensory component, is nociceptive in nature and associated with tissue damage; it is caused by direct activation of peripheral nociceptors and by inflammation.[2] Nociceptive pain is classically managed with the use of opioids, non-steroidal anti-inflammatory drugs (NSAIDs) and local anaesthetics.[3] Despite being effective drugs for the treatment of acute pain,[2] the use of opioid analgesics may be limited by well-known side effects, such as excessive sedation, nausea and vomiting and urinary retention,[3] especially when given neuraxially.[4] While NSAIDs are commonly and successfully used for the treatment of mild-to-moderate pain, they can be potentially be associated with harmful drug effects, such as gastrointestinal, hepatic and renal toxicities.[2]

The search for complementary or alternative analgesic drugs for acute postoperative pain management aims at identifying treatments that are associated with fewer side

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effects seen with traditional treatments, while accomplishing the goals of adequate perioperative pain management. There is a particular need for oral analgesics that can be prescribed for acute pain in patients that are discharged from the hospital. Multimodal analgesic regimens involve the use of different classes of drugs to provide superior pain relief and is the standard of care for many surgical populations.[1] Gabapentin, a drug originally developed as an anticonvulsant, is also used for its analgesic properties.[3,5–8] Being associated with mild side effects, it is a treatment option as part of a multimodal analgesic regimen with more traditional pain management strategies.[1] Several reports and meta-analyses of the use of gabapentin for acute postoperative pain management in humans show promising and encouraging results.[3,9–12] In the veterinary literature, the evidence is limited with mixed results.[7,8,13]

Pain assessment in veterinary medicine is challenging. The short form of the Glasgow Composite Measure Pain Scale (GCMPS-SF) is a validated, multifactorial, clinical measurement for acute pain in dogs.[2,14] This scoring system allows for repeatable assessments of specific behaviours and provides a means to consistently assess the need for rescue analgesia.[14,15] Pressure platform gait analysis is a sensitive and objective assessment of limb function after orthopaedic procedures in dogs and cats.[16,17] With pressure platform gait analysis, limb function data from all limbs can be gathered with the animal standing over a fixed period of time allowing for simultaneous evaluation of all limbs. This technique has been previously used to evaluate the efficacy of postoperative analgesic techniques in dogs after surgery for cranial cruciate ligament disease (CCLD).[15,16,18]

Given the need for additional oral analgesics in the dog and the limited and mixed evidence investigating gabapentin, we elected to evaluate the effectiveness of gabapentin as an analgesic adjuvant, combined with carprofen, for the control of postoperative pain after tibial plateau levelling osteotomy (TPLO) surgery, using the GCPMS-SF and pressure platform gait analysis as outcome measures. We tested the null hypothesis that analgesic intervention (carprofen or carprofen plus gabapentin) would not influence outcome measures.

Materials and Methods

Animals

This study was approved by the University of Minnesota Institutional Animal Care and Use Committee, and written informed client consent was required prior to enrolment into the study. Twenty adult dogs of various breeds and ages with complete, unilateral CCLD were enrolled in the study. Dogs were assessed to be healthy other than unilateral lameness, knee pain and prominent femoral–tibial instability based on physical examination and laboratory analysis including haematology and blood chemistry. For the purposes of this study, only dogs where owners elected caudomedial arthrotomy and release of a normal medial meniscus were enrolled. Exclusion criteria included dogs weighing less than 15 kg and dogs that had received analgesics, including steroids and NSAIDs within the 3 days prior to assessment.

Study Group

Animals enrolled in the study were randomly assigned using computer generated randomization to one of two postoperative treatment groups and received either carprofen (4.4 mg/kg orally every 24 hours; Rimadyl, Zoetis Inc., Michigan, United States) or carprofen plus gabapentin (Alkem Laboratories Ltd, Mumbai, India) 20 mg/kg, orally, every 8 hours beginning the night prior to surgery and continuing for 14 days postoperatively. Administration of medications began the evening prior to surgery so each dog received one treatment prior to surgery. Outcome measures included subjective pain evaluation via the GCMPS-SF and limb function (per cent of body weight placed on the affected limb over 10 seconds) measured by pressure platform gait analysis. All assessments were performed by investigators blinded to the treatment group (►**Table 1**).

GCMPS-SF

The GCMPS-SF, a validated scale for the assessment of acute postoperative pain in dogs,[19] consists of six behavioural categories and a maximum total score of 24 points was possible: vocalization (4 points), attention to wound (5), mobility (5), response to touch (5), demeanour (6) and posture and activity (5). Each dog was assessed at 11 time points. Scoring was performed the day prior to surgery, at 2pm and 6pm the day of surgery, at 6 am, 12 pm, and 6 pm on days 1 and 2 after surgery, at 6am on day 3 after surgery (the day of discharge from the hospital) and on day 14 ($\pm$ 2 days) after surgery.

Pain assessments were performed by one of two blinded observers, throughout the study period. In an effort to limit variability, the same observer performed all pain evaluations on a patient throughout the study period. If a dog received a GCMPS-SF score more than or equal to 6, rescue analgesia was provided. Rescue analgesia consisted of hydromorphone (0.05 mg/kg) subcutaneously. If a dog required rescue analgesia, the dose was recorded and monitoring continued as scheduled without exclusion from the study. In addition to scheduled assessments, hospital staff monitored each dog hourly. The staff was instructed to contact the pain evaluator if any dog exhibited painful behaviour between pain assessments.

Limb Function Assessment

Limb function was assessed in all four limbs simultaneously by use of a pressure measurement walkway system (Tekscan, South Boston, Massachusetts, United States) as described previously.[15,16,18,20] Prior to each assessment, the system was equilibrated and calibrated according to the manufacturer's specifications. A valid trial consisted of 10 seconds of the dog standing with all weight-bearing feet on the walkway without extraneous movement. The first three valid trials were collected and averaged for data analysis. The percentage of the dog's body weight that was placed on each limb was determined by comparing vertical pressure with the total weight of the dog. Data were collected at 4 pm the day prior to surgery, at 8am on days 1, 2, 3 after surgery and during the recheck appointment 14 $\pm$ 2 days following surgery.

Table 1 Data collection and treatment schedule

Day	Hour	CBC/Chem	Surgery	GCPS-SF	Limb function	Carprofen	Gabapentin
−1	< 8 pm	X		X	X		
	10 pm					X	X
0	6 am						X
	8 am		X				
	2 pm			X			X
	6 pm			X			
	10 pm					X	X
1	6 am			X			X
	10 am				X		
	2 pm			X			X
	6 pm			X			
	10 pm					X	X
2	6 am			X			X
	10 am				X		
	2 pm			X			X
	6 pm			X			
	10 pm					X	X
3	6 am			X			X
	10 am				X		
14	10 am				X		

Abbreviations: CBC/Chem, haematology/blood chemistry; GCPS-SF, Glasgow Composite Pain Scale-Short Form.

Adverse Events

Dogs were monitored throughout the study period for adverse events that may have been caused by the study drug. Events specifically assessed were excessive sedation, regurgitation, vomiting and diarrhoea. Events were classified as mild, moderate or severe and unlikely, somewhat likely, very likely related to the study drug(s). Dogs who experienced severe adverse events were removed from the study.

Anaesthesia and Surgery

Dogs were premedicated with morphine (0.8 mg/kg; Hikma Pharmaceuticals, New Jersey, United States) and acepromazine (0.02 mg/kg; Boehringer Ingelheim, Georgia, United States) intramuscularly. Anaesthesia was induced with propofol (2–6 mg/kg, to effect; Sagent Pharmaceuticals, Illinois, United States) intravenously and maintained with isoflurane (Piramal Enterprises LTD, India) vaporized in 100% oxygen and a fentanyl intravenously constant rate infusion (10 min/µg.kg; Hospira, Illinois, United States). Each dog enrolled in the study had surgery the morning of day 0 of the study. Preoperative radiographs were performed to ensure no pathology beyond CCLD was identified, to document the tibial plateau angle and to ensure the angle was not excessive. Surgery was performed by one of two faculty surgeons (Diplomates of the American College of Veterinary Surgeons) without the use of jig and consisted of a caudomedial approach to the stifle joint. Medial meniscus examination was performed and when indicated a caudal pole meniscectomy was performed or the medial meniscus was released via transection just caudal to the medial collateral ligament. The joint was closed, TPLO was performed, the tissues were closed and postoperative radiographs were taken. No bandage was applied to the limb after surgery. Postoperative analgesia consisted of hydromorphone (0.05 x2009;mg/kg; West-Ward, New Jersey, United States) intramuscularly immediately after surgery and every 6 hours until midnight the day of surgery.

Statistical Analysis

Summary statistics and histograms were computed for each variable (e.g. age, body weight, and sex). This was used to assess data quality (e.g. identification of spurious observations) and distributional assumptions. Preoperative physiologic indices, pain scores and ground reaction forces were compared between treatment groups to verify balance among possible confounding variables. To test for a difference in rescue rates and adverse events between the two treatments, we fit a logistic regression on rescue with treatment as the predictor.

To test for a difference in percentage weight placed on an affected limb, we fit a mixed model on the percentage (averaged over 3 measurements) with treatment, day and their interaction and a random effect for each individual. Covariates for meniscal injury 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, day 3, and day 14. Differences in least squares means from baseline were computed for each day and for the average of the 4 days. Data are expressed as mean ± standard error of the mean. Data were assessed after enrolment of 20 dogs to determine if enrolment of additional cases would continue or if a stopping protocol (no clinically important difference between groups) would be instituted.

Results

Twenty dogs were enrolled and completed the study. There was no difference in body weight, age, affected hindlimb or sex between groups (►**Table 2**). There was no difference in preoperative (GCMPS-SF) or the per cent of body weight placed on the injured limb. Before surgery, (GCMPS-SF) was less than 6 (range: 0–5) in all dogs. After surgery, a (GCMPS-SF) more than or equal to 6 was documented in four dogs, two dogs in each group (20%). No dog required rescue analgesia more than once. All scores more than or equal to 6 occurred the day of surgery. The range of pain scores for dogs requiring rescue analgesia was 6 to 12 out of a maximum score of 24. There was no difference between groups in the number of dogs that required rescue analgesia and there was no difference in pain scores before or after surgery (►**Fig. 1**). No adverse events were documented in any dog.

Table 2 Signalment data for dogs in both study groups

Variables	Carprofen	Carprofen + gabapentin
Sex		
MN	1	2
MI	0	0
FS	8	7
FI	1	1
Affected limb		
Right	4	5
Left	6	5
Weight (kg)	32.58 ± 8.79 (22.7–46.0)	33.53 ± 7.06 (24.5–46.7)
Age (y)	5.55 ± 2.06 (3–10)	5.8 ± 2.57 (3–10)

Abbreviations: FI, female intact; FS, female spayed; kg, kilograms; MI, male intact; MN, male neutered; SD, standard deviation.
Data for weight and age are presented as mean ± SD (range).

There was no significant difference in the percentage of body weight placed on the affected hindlimb between groups at any time during the study (►**Fig. 2**). During the postoperative evaluations, the average limb function on the operative limb was 3.35% (standard deviation = 1.62%) for dogs receiving carprofen + gabapentin and 3.98% (standard

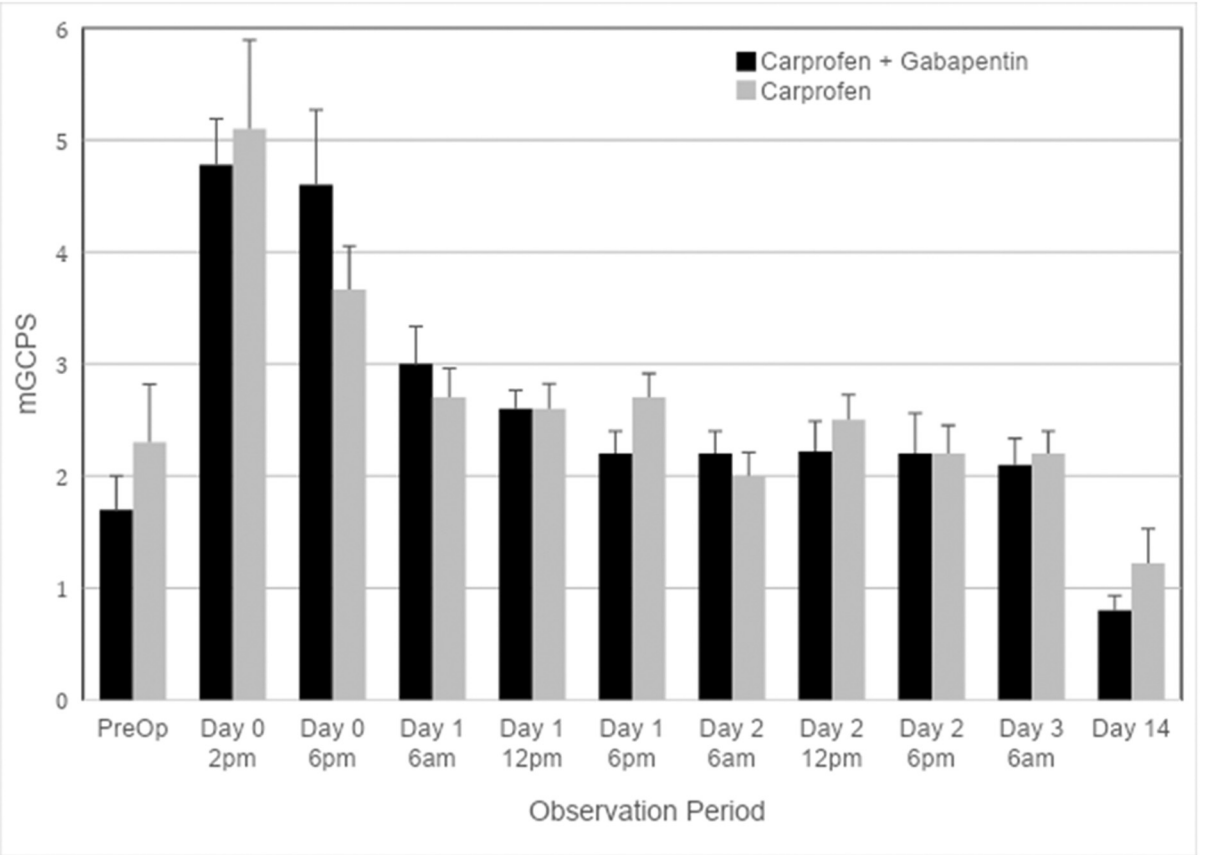

Fig. 1 Modified Glasgow Composite Pain Scores (mGCPS) for dogs in both groups over the study period. No difference at any time period was found between groups. Data are represented as mean ± standard error of the mean.

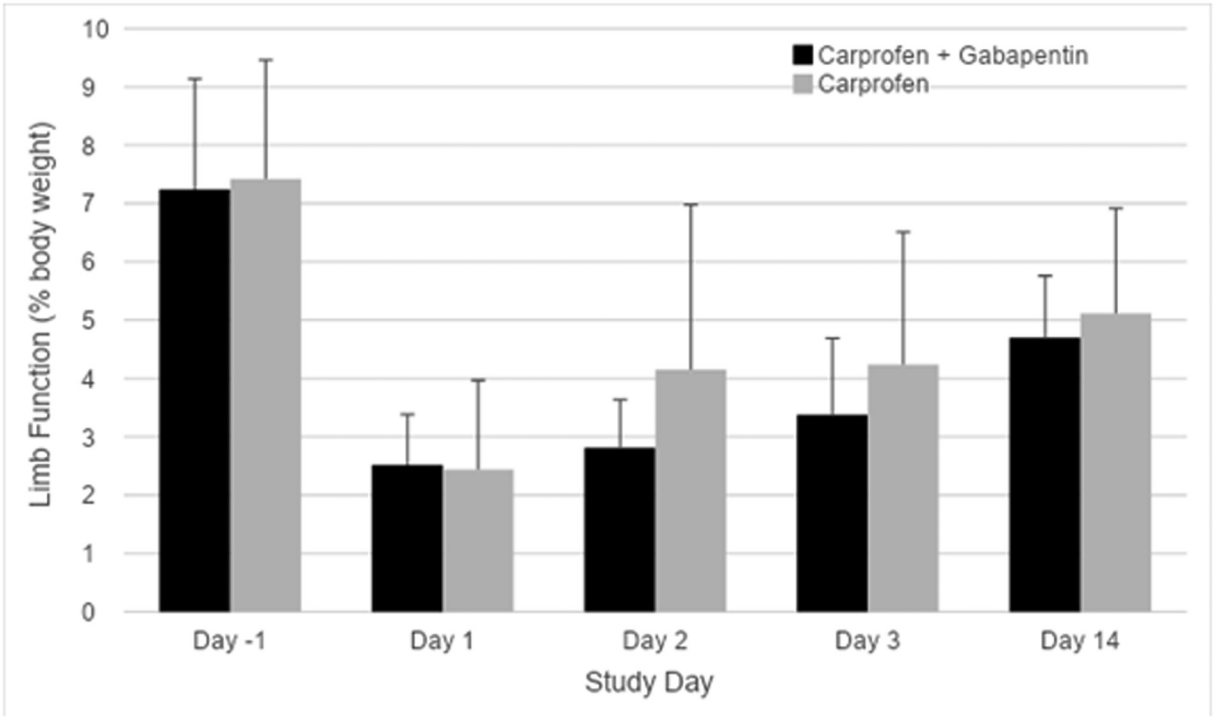

Fig. 2 The percentage of body weight placed on the operated limb, compared with the total amount of weight applied by all limbs during a 10-second period of standing. No difference at any time period was found between groups. Data are represented as mean ± standard error of the mean.

deviation = 1.66%) for dogs receiving only carprofen. Limb function decreased from the preoperative to the postoperative period and increased over time after surgery. The type of meniscal surgery and the surgeon performing the procedure were not found to impact postoperative limb function in the affected hindlimb postoperatively in either group.

Discussion

The results of this study suggest that carprofen plus gabapentin (at 20 mg/kg, orally, every 8 hours beginning the night prior to surgery and continuing for 14 days postoperatively) provides no efficacy advantage over carprofen alone. From these results, we failed to reject the null hypothesis that analgesic intervention (carprofen or carprofen plus gabapentin) would not influence outcome measures.

Appropriate postoperative pain management is an essential part of ethical veterinary care. Pain associated with surgery is most commonly classified as acute nociceptive pain, but neuropathic mechanisms may also be present.[8,10] The addition of drugs with analgesic properties that do not cause undesirable effects that can be associated with more commonly used analgesics, and that may reduce opioid requirements, would be a promising and attractive option for a multimodal perioperative analgesic plan.[3,10] Gabapentin was especially attractive to investigate because it could be given orally to the patient in their home environment with diminished abuse and diversion potential when compared with opiates.[21] Gabapentin can be anti-hyperalgesic, possibly reducing central sensitization as it reduces hyperexcitability of dorsal horn neurons.[9] Central sensitization is a known and important factor in chronic pain states, but it may also be present after trauma and surgery.[13] Despite the sparsity of evidence for the use of gabapentin in dogs, its clinical use is common.[22]

Although there are inconsistencies in recommendations, gabapentinoids are used to control chronic pain conditions in both humans and animals, but interest has grown in assessing their efficacy in controlling postoperative pain. In people, the use of gabapentin for acute nociceptive pain conditions has been shown to reduce opioid requirements, especially when combined with an NSAID.[3,8,13,23] Systematic reviews have found that most studies attribute lower opioid consumption and pain scores to the perioperative use of gabapentin.[1,9–11] However, others have concluded that results have been heterogeneous depending on the type and severity of pain, and that the absolute effects observed may have been overestimated by publication bias in favour of the analgesic effect of gabapentin.[12] In a recent systematic review and meta-analysis of the perioperative use of gabapentinoids for management of postoperative pain in humans,[24] the authors found that there were no clinically significant differences in postoperative acute, subacute and chronic pain with the use of gabapentinoids; they also found that their use was associated with a higher incidence of adverse events (dizziness and visual disturbance). The authors conclusively stated that the routine use of gabapentinoids for managing acute postoperative pain in adults is not recommended.[24] Translation of these findings to veterinary patients is challenging because of potential differences in drug pharmacokinetics and pharmacodynamics.

In our study, the perioperative use of gabapentin combined with an NSAID (carprofen) after TPLO surgery in dogs did not improve postoperative pain, as assessed by a validated pain scale and gait analysis, when compared with carprofen alone. This result agrees with previous studies that assessed the adjunctive effect of gabapentin for postoperative pain control in dogs submitted to other types of surgery. Wagner and colleagues found no significant differences when gabapentin (10 mg/kg, orally, the day before surgery, followed by 5mg/kg, orally, every 12 hours, for 3 days) was used as an adjunct perioperative analgesic for forelimb amputation[8]; similarly, Aghighi and colleagues found no differences in pain scores or rescue analgesia requirements after intervertebral disc surgery in dogs when gabapentin (10 mg/kg, orally, every 12 hours) was added to the opioids used as the standard of care.[7] However, in a study assessing the use of gabapentin as an adjuvant in dogs undergoing mastectomy, Crociolli and colleagues found a significant difference in rescue analgesia requirements,[13] supporting a role for gabapentin (10 mg/kg, orally) in acute postoperative pain management. Additionally, gabapentin, 20 mg/kg, administered orally, 2 hours prior to maintenance of anaesthesia with isoflurane, has been shown to reduce the minimum alveolar concentration of isoflurane in dogs[25]; however, this effect may simply be associated with the drug's depressant effect on the central nervous system.

It is important to note that, according to the pharmacokinetic data available for gabapentin in dogs,[6] a dose of 10 to 20 mg/kg, every 8 hours, would be needed to maintain adequate plasma level of the drug. In previous studies where no significant differences were found,[7,8] gabapentin administered at lower doses and/or at greater time intervals (every 12 hours) could have been inadequate to maintain target plasma levels. This could explain the lack of significant findings in those studies. However, Crociolli and colleagues used the same dosing regimen as the two previous studies (every 12 hours) and found a significant reduction in opioid rescue requirements.[13] Based on data obtained by Kukanich and Cohen,[6] we used a dosing regimen of gabapentin every 8 hours and found no analgesic benefit of gabapentin. These differences could be from heterogeneity in study populations and study design.

It is possible that the degree of pain control provided by an NSAID could have contributed to the lack of additional analgesia provided by gabapentin. Lewis and colleagues have previously demonstrated that for stifle joint surgery in dogs, patients that received only morphine preoperatively and an NSAID postoperatively had a mean GCMPS-SF of 2.8 ± 2.0; no animal in their study had a GCMPS-SF pain score more than 7.[26] In our study, all patients were given carprofen the day prior to surgery and continued, every 24 hours, for 3 days; our patients were premedicated with morphine and received one dose of hydromorphone postoperatively. Thus, it is not surprising that the rescue rate was low and that subjective assessment (using GCMPS-SF) could not demonstrate subtle differences between groups. However, there were also no differences in our objective assessment of limb function and the dogs that received carprofen and gabapentin actually had a lower average mean peak pressure in the operated limb.

This randomized clinical trial has limitations with respect to its generalization to a larger population. First, surgery was limited to two surgeons using a very similar surgery. It is possible that alternative surgical techniques could have impacted the results. We used relatively strict inclusion criteria, and while this allowed us to answer a specific question, it does not allow us to generalize to a different population. For example, we did not include dogs under 15 kg because, at the authors' institution, in dogs this size owners more often elect, and the surgeons often perform a different technique than the one investigated. It is possible that different results would be found in a population of dogs under 15 kg. In an effort to avoid unnecessarily including animals in a clinical trial, statistical evaluation was performed after 10 dogs per group completed the study. While this decreases the statistical power of the study, our findings suggest that enrolling more animals would have unlikely changed the significance or clinical importance of the results. To be more specific, after studying 10 dogs per group, dogs given gabapentin had approximately 15% decreased limb function compared with the standard of care group. To achieve a statistical difference with 20 dogs per group (assuming the standard of care group remained the same), the next 10 dogs receiving gabapentin would have had to put approximately 50% weight on their operated limb. Since only one of ten of the first dogs achieved this level of limb function, we felt it would be very unlikely that level of limb function would be the average in the next 10 dogs studied. We did not measure plasma drug levels. The dose used, while commonly used in our hospital and within the published dose range known to achieve effective plasma levels in humans,[6] may have been too low to achieve adequate results in our patient population.

Pain assessment in veterinary patients remains a crucial but challenging task. Although pain assessment tools are available to facilitate performing this task, the level of subjectivity and interpretation still leaves room for error. Multidimensional tools, as the one used in our study, take into account behavioural aspects of the patients being assessed. Animals will likely have varying behaviours, some of which will be influenced by the level of pain, but others will also likely be influenced by stress, anxiety and previous experiences, both before and after hospitalization. Complementing subjective assessment with an objective outcome measure provides additional insight into the patient's level of pain by delivering a description of clinical function in the operated limb.

We found that the addition of oral gabapentin (20 mg/kg, orally, every 8 hours beginning the night prior to surgery and continuing for 14 days postoperatively) did not improve subjective or objective outcome measures.

Conflicts of Interest

None declared.

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