Preliminary evaluation of the effects of grapiprant compared with carprofen on acute pain and inflammation following ovariohysterectomy in dogs

Brittany L. Southern, DVM1*; Sarah M. Long, DVM2; Danielle N. Barnes, DVM2; Hiroko Enomoto, DVM3; Kristen M. Messenger, DVM, PhD2

1Departments of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC
2Molecular Biomedical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC
3Population Health and Pathobiology, College of Veterinary Medicine, North Carolina State University, Raleigh, NC

*Corresponding author: Dr. Southern (bsouthern@ufl.edu)

OBJECTIVE
To compare the analgesic efficacy of grapiprant to carprofen for the treatment of postoperative pain and inflammation in dogs following ovariohysterectomy.

ANIMALS
12 purpose-bred adult sexually intact female Beagles.

PROCEDURES
Dogs were randomly assigned to 1 of 2 treatment groups: grapiprant (2 mg/kg, PO; n = 6) or carprofen (4.4 mg/kg, PO; n = 6), 1.5 hours prior to ovariohysterectomy (OVH) and every 24 hours afterward for 3 total doses. An ultrafiltration probe was placed within the OVH incision to collect interstitial fluid (ISF). Pain and inflammation were assessed by masked investigators via mechanical nociceptive threshold testing and the short form of the Glasgow Composite Pain Scale before drug administration and at multiple time points for 72 hours following dosing and surgery. ISF samples were collected at the same time points to assess prostaglandin E₂ concentrations at the site of inflammation.

RESULTS
In both groups, pain scale scores were highest in the immediate postoperative period and decreased over time. In both treatment groups, there were significant (P = 0.003) differences in mechanical nociceptive threshold results over time when compared with baseline, but there was no difference between groups. Prostaglandin E₂ concentrations in ISF were higher in dogs receiving grapiprant compared with carprofen (P < 0.001). One dog in the carprofen group required rescue analgesia.

CLINICAL RELEVANCE
Results of this preliminary study suggested both carprofen and grapiprant may be effective for postoperative pain following OVH in dogs; however, additional studies are warranted to determine grapiprant’s effectiveness in a larger and more diverse population of dogs.

Carprofen, a preferential cyclooxygenase (COX)-2 inhibitor, is a commonly used NSAID in dogs; however, many dogs experience side effects and adverse reactions secondary to inhibition of homeostatic eicosanoid production.1-3 Side effects range from mild to severe and can include inappetence, vomiting, gastrointestinal ulceration or hemorrhage, hepatic or renal injury, and coagulopathy, potentially leading to death.3,4 Opioids also provide analgesia, but their use may not adequately address the pain associated with inflammation. In addition, the risk for pet owner diversion and abuse has led to modifications in opioid use within the health professions, including veterinary medicine.5 Due to these opioid modifications and risk of life-threatening side effects of NSAIDs, safe alternative analgesic options for dogs should be explored.

Grapiprant, a piprant EP₄ prostaglandin E₂ receptor antagonist, is a novel anti-inflammatory drug that acts further downstream in the arachidonic acid cascade, avoiding the inhibition of eicosanoid production by blocking only the specific receptor involved with prostaglandin E₂ (PGE₂)-induced pain.1₆,7 In contrast to traditional COX-inhibiting NSAIDs, piprants maintain the homeostatic functions of prostaglandins8 and may have an improved margin of safety when compared to traditional NSAIDs.

Grapiprant is currently FDA approved for the treatment of pain associated with canine osteoarthritis9,10; however, the current literature10,11 regarding...
the efficacy of grapiprant is contradictory. The use of grapiprant for the treatment of acute, soft tissue pain and inflammation in dogs has not been assessed and would be considered extralabel use of the drug. One study in rabbits compared the efficacy of grapiprant with meloxicam in an acute inflammatory model using carrageenan; however, no similar studies have been performed in dogs.

The primary objective of this preliminary study was to compare the analgesic efficacy of grapiprant to carprofen for the treatment of postoperative ovariohysterectomy (OVH) pain and inflammation in dogs. The secondary objective was to assess the anti-inflammatory activity of grapiprant and carprofen by quantification of PGE2 concentrations at the site of inflammation. We hypothesized that grapiprant administration would result in reduced pain scores, that there would be no difference in pain when comparing experimental groups, and that PGE2 concentrations at the site of inflammation would be higher in dogs receiving grapiprant than in dogs receiving carprofen.

Materials and Methods

Animals

Twelve adult sexually intact female Beagles, 2 to 5 years of age and weighing 7.8 to 11.0 kg were used in the study. All dogs were considered healthy on the basis of annual physical examinations, blood chemistry, and hematology panels. Dogs were members of the university-owned colony; previous use included noninvasive ophthalmologic examination procedures and noninvasive veterinary student training courses.

Dogs were transported to their temporary housing space 72 hours prior to surgery to allow acclimation to the temporary housing. During the acclimation period and during the study, dogs were individually housed in runs with visual, auditory, and olfactory contact with a conspecific in the next enclosure. Supervised paired access between dogs was provided daily. An elevated cot with blankets was provided as additional bedding material postoperatively. A commercially available dry dog food (Exclusive Adult Dog; PMI Nutrition) was fed twice daily with ad libitum water. Room temperature was maintained between 17.8 and 23.3 °C, with a 12:12-hour light-dark cycle. For sample collections occurring during the dark cycle, lights were turned on briefly for collection then immediately turned off. Two chew toys per dog were provided at all times for enrichment. The study protocol was reviewed and approved by the North Carolina State University Institutional Animal Care and Use Committee.

Study design

Dogs were assigned via coin toss to 1 of 2 treatment groups: oral grapiprant (2 mg/kg; n = 6) or oral carprofen (4.4 mg/kg; n = 6). 1.5 hours prior to OVH and every 24 hours afterward for 3 total doses. Doses were chosen according to the FDA-approved package labeling; however, the indicated use for grapiprant for soft-tissue perioperative pain was extralabel. A sample size calculation was performed (Graphpad StatMate 2.0) using PGE2 data from a pilot study with 2 dogs, with the assumption of large individual variation in PGE2 concentrations. The calculation, designed to detect a difference in PGE2 between treatment groups, assuming a difference in the mean of 7,500 pg/mL with an SD of 5,000 pg/mL and a power of 0.8, revealed that 8 dogs/treatment group would be needed. However, 16 female dogs were not available from the university-owned colony; thus, 12 dogs were enrolled.

Surgery

Dogs were fasted and received oral maropitant (2 mg/kg) the evening prior to surgery. Maropitant was provided to minimize emesis of the study drug, as vomiting is a potential side effect of NSAIDs and opioids. The administered dose was not classified as analgesic, based on a study by Boscan et al. The morning of surgery, baseline pain assessments were collected in the temporary housing space. The observer performing assessments was masked to drug group assignments. After baseline collections, the dogs were orally dosed by a second, unmasked individual approximately 1.5 hours prior to surgery. This time point was chosen based on the pharmacokinetics of grapiprant, which would have an anticipated time to maximum plasma concentrations between 1 and 2 hours postadministration. Similarly, maximum plasma concentrations are achieved in 1 to 3 hours after oral administration of carprofen.

Dogs were then moved to the surgery preparatory room. All dogs in both treatment groups were premedicated with buprenorphine (0.01 mg/kg, SC). An IV catheter was placed in the cephalic vein. General anesthesia was induced with propofol (6 mg/kg, IV, to effect), and dogs were orotracheally intubated and then maintained on isoflurane inhalant delivered in 100% oxygen. Dogs were instrumented with monitoring equipment (Datascope Passport 2; Mindray) to assess body temperature, heart rate, respiratory rate, electrocardiography, capnography, blood pressure, and oxygen hemoglobin saturation. The hair in the cranioventral neck region was clipped and removed, skin was aseptically prepared, and a single-lumen long line indwelling catheter (Long Line Catheter; MILA International) was placed into a jugular vein using the modified Seldinger technique. The catheter was sutured into place to facilitate collection of blood during the course of the study. The incision was covered with antimicrobial drape adhesive (Ioban Antimicrobial Incise Drape; 3M) and a light soft padded bandage using cast padding, cling wrap, and a self-adhering bandage (VetRap; 3M) was placed around the neck to protect the catheter. The hair on the abdomen from xiphoid to pubis was clipped and removed, and the skin was aseptically prepared using chlorhexidine and alcohol. The dogs were briefly removed from monitoring equipment and isoflurane, carried to the surgical suite, and again placed on isoflurane in 100% oxygen and monitoring equipment. The abdominal surgical site was again
aseptically prepared, and the dogs were administered lactated Ringer solution at 10 mL/kg/h, IV.

Using aseptic technique, 2 veterinarians with experience in performing the surgical procedure performed routine OVH via midline laparotomy. Each veterinarian was masked to treatments, assigned 6 dogs, and had 3 dogs each from both treatment groups. Following OVH, the linea alba was closed in a simple continuous pattern with simple interrupted sutures placed when needed, using polydioxanone suture. In order to quantify PGE<sub>2</sub> levels at the site of inflammation, a 6-cm sterile ultrafiltration (UF) sampling probe (RUF-3-12 In-Vivo Ultrafiltration Sampling Probe; Bioanalytical Systems Inc) was placed along the linea alba, covered in a protective red casing material to prevent the dialysis fibers from folding (Figure 1). The subcutaneous tissues and skin were closed together over the protective casing in an intradermal pattern using 2-0 polydioxanone. Once three-quarters of the skin was closed, the protective casing material was gently removed using forceps. The remaining skin was then closed in the same manner. The final knot was tied outside of the skin to prevent accidental puncture of the probe or tubing by the suture needle. The probe's nonpermeable conducting tubing was connected to a needle adapter and evacuated tube without additive. In order to prevent trauma to the probe, the conducting tubing was sutured to skin in the perineal region by using a piece of tape as a butterfly.

Dogs were recovered from anesthesia, the incision site was covered with a nonadhesive pad, and a stockinette was placed around the abdomen to protect the tubing and evacuated tube. A soft no-bite collar was placed around the neck bandage to prevent self-induced chewing or licking at the incision site. Dogs were returned to their temporary housing space, with vital parameters monitored every 5 minutes until returning within reference ranges. Once the dogs were completely recovered from anesthesia, pain assessments and interstitial fluid (ISF) collections continued at specific time points, starting at 2 hours postsurgery, which was equivalent to approximately 4 hours postdrug administration.

### Pain assessments

To compare the analgesic effects between drugs, the short form of the Glasgow composite pain scale (CMPS-sf) and mechanical nociceptive threshold (MNT) testing were used as pain assessment tools. Both assessments were performed by 1 of 2 masked observers prior to initial drug administration for baseline data and then at multiple time points (4, 6, 8, 12, 18, 24, 32, 40, 48, 60, and 72 h) after the initial drug dose once dogs recovered from surgery. Assessments were performed in the same order at each time point.

In order to allow the masked observer the opportunity to observe and subjectively assess the dog upon entering the housing space, CMPS-sf scoring was performed first. This scale included 30 descriptor options within 6 behavioral categories with a possible maximum score of 24 points. Within each category (vocalization, attention to wound, mobility, response to touch, demeanor, and posture or activity), the descriptors were ranked numerically according to their associated pain. If dogs were nonambulatory due to residual anesthesia and sedation, the CMPS-sf pain assessment was not performed, which was relevant only for the 4-hour time point postdrug administration (approx 2 h postoperatively). Pilot data showed our purpose-bred research dogs often scored higher in categories where actions may be associated with nervousness (ie, in section B of CMPS-sf, which describes visual observation of the dog when a lead is placed, as many of these dogs were not trained to a lead and refused to walk; and in section D, which subjectively describes overall demeanor such as being nervous or restless), so a score of > 10/24 was the defined endpoint for requirement of rescue analgesia. Because the validated scoring system was modified with a higher cutoff than the scale recommends, an additional subjective assessment for the provision for analgesia was included, where if the dog was clinically judged as painful, regardless of CMPS-sf scores, it received buprenorphine (0.01 mg/kg, IV)<sup>17,18</sup> and was reassessed at each following time point.

![Figure 1](image-url) —Photographs showing placement of ultrafiltration probe along linea alba during ovariohysterectomy in a Beagle. A—White probe covered by the protective red casing material (*), which was removed just prior to completion of skin closure. B—Clear nonpermeable conducting tubing (†) exiting the incision and attached to the needle adapter and evacuated tube.
After the CMPS-sf was assessed, blood was collected to determine drug plasma pharmacokinetics. Two milliliters of blood were aseptically removed from the jugular sampling catheter using a syringe. An additional 2 mL of blood was removed and immediately placed in a lithium heparin vacutainer tube. The original, unclotted blood sample was returned to the dog via catheter followed by a 2-mL saline (0.9% NaCl) flush. The catheter was flushed with 3-mL heparinized saline solution every 24 hours. Blood samples were collected at baseline prior to the initial drug dose and at multiple time points (15 min, 30 min, 60 min, 90 min, 2 h, 4 h, 6 h, 8 h, 12 h, 18 h, 24 h, 32 h, 40 h, 48 h, 60 h, and 72 h) after drug dosing. Results of these data analyses are not reported here.

A handheld pressure algometer (SMALGO Algometer; Bioseb) was used to assess MNT. The dog was laid in left lateral recumbency with minimal restraint, and the stockinette and nonadhesive pad covering the incision site were removed. Once the dog was relaxed, the algometer’s round, flat steel stimulator probe was gently placed at the center of the incision, on the right lateral side approximately 1.5 cm from the incision. Steadily, increasing pressure was then applied until a defined response from the dog occurred. The dog was not restrained in order to show an accurate response. This endpoint response included turning of the head toward the algometer or individual performing the test, abrupt shaking of legs, deliberate escape movement away from the device, vocalization, or attempts to bite or scratch the device. Once the response occurred, the algometer was immediately removed from the animal and the pressure in units of grams was visualized on the device. This pressure was recorded as the MNT. The MNT test was performed 3 times per assessment, with 1 minute of rest in between. The mean MNT reading was used in data analysis.

**PGE₂ analysis**

In order to quantify PGE₂ levels at the site of inflammation, an in vivo UF sampling probe was placed within the incision to allow collection of ISF at multiple time points (4, 6, 12, 18, 24, 32, 40, 48, 60, and 72 h) after first dosing and surgery. Due to lapse in time between initial dosing (1.5 h prior to surgery) and probe placement, the first ISF sample was collected at 6 hours for the majority of dogs.

In vivo UF previously demonstrated measurements of drug and PGE₂ concentrations within ISF at the site of inflammation in dogs.[21] The probe in our study consisted of 3 loops of hollow dialysis fibers to allow filtration up to 30,000 Da from surrounding tissues. The hollow dialysis fibers were connected to a nonpermeable conducting tube, needle adapter, and evacuated tube without additive as a vacuum and collecting source (Figure 1). After blood collection at each time point for data collection, the evaluated tube was removed from the needle adapter and the tube weight was recorded. Using a pipette, the ISF was removed from the evacuated tube, collected into Eppendorf tubes, and stored at −80 °C until processing. A new evacuated tube was placed on the needle adapter. PGE₂ in ISF was quantified using a commercially available ELISA kit (Cayman Chemical) following the manufacturer’s instructions. All samples were quantified in duplicate per time point, and values were averaged per animal.

At the end of study, the unsedated dogs were placed in lateral recumbency, and the conducting tube connected to the UF probe was gently pulled at the caudal end of the incision in order to remove the UF probe from underneath the skin. The jugular catheters were removed, and all dogs were returned to their original housing facility and remained in the university-owned colony for continued teaching use or until adoption at a later date.

**Statistical analysis**

All statistical analyses were performed using a commercially available software program (Prism Version 9.0; Graphpad Software Inc). Data were tested for normality using the Shapiro-Wilk test. The MNT and PGE₂ in ISF data were analyzed using a 2-way ANOVA and Šídák test for multiple comparisons. The administration of rescue analgesia data was analyzed using the Fisher exact test. Values of $P \leq 0.05$, adjusted for multiple comparisons where applicable, were considered significant for all tests.

**Results**

All Beagles completed the study. ISF was successfully collected from all dogs, with an occasional missed sample from 10 of 12 dogs, which occurred due to probe tubing occlusion, kinking, loss of vacuum source secondary to evacuated tube removal, or complete probe removal by an active dog.

None of the dogs in the grapiprant group required rescue analgesia. One dog in the carprofen group (1/6) required rescue analgesia 8 h after initial drug administration. The CMPS-sf score was 8/24; however, the dog was still deemed as painful by the blinded observer. This dog displayed nervousness during all interactions and appeared to have unrelated lumbosacral pain post-OVH. Rectal examination findings and radiographs were unremarkable, and clinical signs resolved by 40 hours after initial drug administration. The dog was assessed at the next scheduled time point; however, the score was not included in data analysis due to the residual sedation from rescue analgesia and sedation used for radiography and rectal exam. Because several other assessments on this dog were collected out to 72 hours beyond the duration of rescue, the remainder of this dog’s data was still included in the results.

Due to the small sample size, number of repeated time points, and likelihood for type II error, no statistical analysis was performed on the numerical CMPS-sf scores. Scores were highest in the immediate postoperative period (the first 8 to 12 h after dosing) and decreased over time in both groups (Figure 2). There was a significant ($P = 0.003$) decrease over time on MNT levels ($P = 0.0028$) but not an effect...
of treatment (P = 0.11). MNT levels were significantly lower at 6 (P = 0.003), 8 (P = 0.002), 12 (P = 0.016), 24 (P = 0.024), 32 (P = 0.030), 40 (P < 0.001), 48 (P = 0.007), 60 (P = 0.008), and 72 hours (P = 0.002) when compared to baseline prior to surgery for both treatment groups (Figure 3). PGE₂ concentrations in ISF were significantly higher in dogs receiving grapiprant compared with carprofen (P < 0.001; Figure 4).

When multiple comparisons were assessed, significant differences were found for time points between 6 and 40 hours after initial drug administration. The adjusted P values were 0.007 at 6 hours, < 0.001 from 12 to 24 hours, 0.002 at 32 hours, and 0.026 at 40 hours. Administration of carprofen resulted in a significant decrease in PGE₂ concentrations compared to grapiprant at these time points.
Discussion

Our objective assessment of pain, the MNT data, showed no difference between the 2 treatment groups in this study. After OVH, MNT levels were significantly lower at most time points compared to baseline for both treatment groups, supporting previous evidence\(^{22–24}\) that OVH is a painful procedure despite preemptive multimodal analgesia with NSAIDs and opioids. Acknowledging that pain is associated with this procedure is important for dog owners and clinicians alike, as OVH is often considered as a “routine” procedure with minimal complications and often, minimal outpatient analgesia. Some canine patients are poor candidates to receive NSAIDs due to their potential side effects; therefore, additional analgesic options in dogs should continue to be explored, and pain associated with OVH procedures should be treated using a multimodal approach.\(^{25}\) Indeed OVH is considered a major procedure in dogs and is associated with pain in dogs.\(^{22–24}\)

No previous published studies have compared the use of grapiprant to traditional NSAIDs for acute soft tissue pain in dogs; however, at least 2 other publications\(^{11,26}\) have found that grapiprant was inferior to traditional NSAIDs in acute synovitis models in dogs. The outcomes and assessments in the synovitis model studies primarily involved force plate-derived data, which are more objective measures of pain. In the present study, we attempted to utilize the CMPS-sf to obtain additional comparisons of pain control following OVH; however, this tool is subjective in nature and has limitations to its use in different settings. While multiple acute pain assessment tools used in dogs exist, including numerical rating scales, visual analogue scales, simple descriptive scales, and other behavior-based scales such as the Colorado State University Acute Pain Scale,\(^{27}\) the CMPS-sf is the only validated acute pain assessment tool in dogs.\(^{20,28}\) This tool was created for and validated in the client-owned dog population; it was not designed for use in purpose-bred research dogs. To our knowledge, there are no validated acute pain scoring tools available for use in purpose-bred dogs. Thus, we acknowledge that the CMPS-sf was modified from its original design in the present study, which is considered a limitation in our ability to utilize these data. While statistical comparisons were not made due to these limitations, we found that scores were highest immediately after OVH and decreased over time, which has also been documented in studies\(^{20,29}\) of client-owned dogs undergoing soft tissue procedures.

The behavioral expression of pain is influenced by many factors, including breed, age, health, gender, anxiety, and fear.\(^{28}\) The behavior of purpose-bred dogs used in research can vary from extreme stoicism to extreme anxiety, especially when compared to client-owned pet dogs who often experience greater socialization during critical developmental stages. Although the Beagles in the present study were generally well-handled, acclimated to the humans involved in the study, and received frequent socialization with other dogs and animal care staff, they displayed anxious behavior and the postoperative scores in the CMPS-sf category referring to their

![Figure 4](image-url)

Figure 4—Prostaglandin E\(_2\) (PGE\(_2\)) concentrations in interstitial fluid for the dogs of Figure 2. *Significant (P ≤ 0.05) difference between treatment groups. See Figure 2 for remainder of key.
overall demeanor were high. In fact, baseline scores were above 0 for 4 of the 12 dogs, due to higher scores in sections B and D of the CMPS-sf, which describe visual observation of the dog with a lead and overall demeanor, respectively. The influence of demeanor in purpose-bred dogs was considered important during a preliminary study and has been reported in other literature as well. Notably, the baseline and postoperative OVH mean pain scores of the dogs in the present study were indeed higher than mean pain scores in a similar study using client-owned dogs. The CMPS-sf recommends analgesic intervention at a score of ≥ 6/24; however, based on results from a pilot study and our previous experience with performing acute pain studies in purpose-bred dogs, a higher score of > 10/24 was chosen as the endpoint for intervention. Alterations to the intervention level have been described, specifically in reference to better reflect the needs of a certain population of dogs. In our study, if the masked observer felt that analgesic intervention was necessary despite a score of > 10 or less, rescue analgesia was administered to the dog and the dog was reassessed at the next time point. Because the rescue analgesia was only expected to be efficacious for a few hours, and the assessments extended to 72 hours, the single dog requiring rescue was included in the study.

A more objective assessment of analgesic efficacy in this study was the use of pressure algometry. Dogs in the carprofen group had higher MNT values at baseline compared to dogs in the grapiprant group (over twice the threshold, in grams), but a significant difference was not detected in these values. Compared to the baseline values, MNT decreased over time at nearly all time points tested out to 72 hours, a finding that has been corroborated in studies by other investigators. Quantitative sensory testing, such as the use of pressure algometry to collect MNT data, is one of the most commonly used methods to assess pain sensitivity through application of a standardized stimulus to a peripheral tissue and the recording of a subject’s response. The MNT was still significantly lower than baseline at the 72-hour time point in both groups, possibly due to hyperalgesia or anticipatory behavior by the dogs. The latter has been previously demonstrated in normal dogs. Hyperalgesia due to peripheral sensitization driven by circulatory proinflammatory or other pain-promoting substances has been demonstrated and could indicate that inflammation and tissue injury were still present 72 hours after surgery. However, because the CMPS-sf scores ranged between 0 and 1 by 72 hours, we believe the observation in MNT was due to a learned response and not hyperalgesia. Recording of any threshold in nonverbal species is dependent on reactions to the stimulus. In the present study, the dogs subjectively appeared to acclimate to the pressure algometer. Because it was used at multiple time points over 72 hours, some dogs may have learned that their response would lead to removal of the device. By the third day (72 h), some of the dogs were not as tolerant of being placed in lateral recumbency, which may have also affected the algometer scoring. The creation of a tool to evaluate acute pain in purpose-bred research dogs is still needed to better assess how pain is displayed in this unique population of dogs. In the present study, a negative control group without analgesia, or even a sham group without any surgery, may have helped differentiate between pain and anxiety, as well as help determine which drugs provided effective analgesia. However, due to the ethical concern of withholding analgesia in a painful procedure and limitations in numbers of available dogs, these groups were not included in this study.

PGE2 was significantly higher at the site of inflammation in the grapiprant-treated group than the carprofen-treated group at time points between 6 and 40 hours after drug administration, which suggests that the physiological activity of PGE2 is indeed preserved in the dogs receiving grapiprant. Carprofen administration resulted in decreased PGE2 production for the duration of the 72-hour study period, although there was not a negative (untreated) control group to compare these results. To the authors' knowledge, this is the first study to quantify PGE2 concentrations at an incision site in dogs; the use of UF probes to collect biomarkers of inflammation at surgical sites of inflammation and pain could be utilized in future study designs as a minimally invasive technique to assess the anti-inflammatory activity of different compounds. Grapiprant did not suppress the PGE2 biosynthesis, which may avoid the adverse effects that can result from inhibition of active physiological PGE2. Because it does not reduce PGE2 production, grapiprant could be an alternative drug option for dogs who experience serious side effects of traditional NSAIDS. Further studies on analgesic efficacy for acute inflammatory pain using grapiprant are still warranted.

The present study had limitations that warrant discussion. First, our sample size was small and there was potential for a type II statistical error to occur, such that we could not detect a difference between groups for our assessments. We performed an a priori power analysis based on PGE2 data collected in a small pilot study. Our a priori analysis suggested that 16 dogs would be needed to detect differences in this biomarker; however, we were still adequately powered to detect significant differences in PGE2 despite using fewer dogs. We did not perform an a priori sample size calculation for the other outcomes assessed in this study; thus, we cannot exclude the possibility of a type II error in the other outcomes we assessed. In addition, use of a coin toss as the tool for group assignment is a concern for randomization as it is subject to human judgment; however, we did ensure the pain assessments in groups were blinded.

Secondly, this study could have been strengthened by having the same person perform all surgeries. Tissue-handling techniques, the duration of surgical procedure, and the size of the incision can vary between surgeons, which may lead to variable degrees of postoperative inflammation. In considering this limitation, each masked veterinarian...
performed the OVH in the same number of dogs in each treatment group in order to minimize any influence of the veterinarian performing the surgery. A further limitation could be the use of preoperative maropitant for the prevention of emesis. While controversial, maropitant has been suggested to play a role in the reduction of noxious visceral stimulation, specifically ovarian pain in dogs.\textsuperscript{15,16} However, the dosing used in the present study was much lower than the dose suggested to provide analgesia, and all dogs in both groups received the drug preoperatively; thus, any influence of maropitant on pain assessment would have occurred in both groups equally. Lastly, the lack of a negative control group raises the question of whether either drug provided sufficient analgesia; however, carprofen at the dose administered in this study has been shown to provide effective analgesia after OVH in dogs.\textsuperscript{40}

In summary, we were unable to detect a difference in our subjective pain scores and objective MNT values between grapiprant and carprofen following OVH in dogs. Our findings may be used to design future clinical trials to assess the use of grapiprant to manage postoperative OVH pain in dogs.

Acknowledgments

Funded in part by the Department of Clinical Sciences Firestone Canine Research Endowment at North Carolina State University. Funding sources did not have any involvement in the study design, data analysis and interpretation, or writing and publication of the manuscript.

The authors declare that there were no conflicts of interest.

The authors thank the College of Veterinary Medicine Laboratory Animal Resources staff for their care of the dogs, Dr. Alexandra Carlson for data analysis, Dr. Nneka George for surgical support, and Dr. Penelope Reynolds for assistance with data review and statistical calculations.

References


