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RESEARCH PAPER

Post-operative analgesic effects of butorphanol or firocoxib administered to dogs undergoing elective ovariohysterectomy

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Abstract

Objective To compare the post-operative analgesic effects of butorphanol or firocoxib in dogs undergoing ovariohysterectomy.

Study design Prospective, randomized, blinded, clinical trial.

Animals Twenty-five dogs >1 year of age.

Methods Dogs received acepromazine intramuscularly (IM), 0.05 mg kg^{-1} and either butorphanol IM, 0.2 mg kg^{-1} (BG, $n = 12$) or firocoxib orally (PO), 5 mg kg^{-1} (FG, $n = 13$), approximately 30 minutes before induction of anesthesia with propofol. Anesthesia was maintained with isoflurane. Ovariohysterectomy was performed by the same surgeon. Pain scores using the dynamic and interactive visual analog scale (DIVAS) were performed before and at 1, 2, 3, 4, 6, 8 and 20 hours after the end of surgery by one observer, blinded to the treatment. Rescue analgesia was provided with morphine (0.5 mg kg^{-1}) IM and firocoxib, 5 mg kg^{-1} (BG only) PO if DIVAS > 50. Groups were compared using paired *t*-tests and Fisher's exact test ($p < 0.05$). Data are presented as mean ± SD.

Results The BG required significantly less propofol (BG: 2.6 ± 0.59 mg kg^{-1}; FG: 5.39 ± 0.7 mg kg^{-1}) ($p < 0.05$) but the anesthesia time was longer (BG: 14 ± 6, FG: 10 ± 4 minutes). There were no differences for body weight (BG: 7.9 ± 5.0, FG: 11.5 ± 4.6 kg), sedation scores, and surgery and extubation times (BG: 10 ± 2, 8 ± 5 minutes; FG: 9 ± 3, 8 ± 4 minutes, respectively) ($p > 0.05$). The FG had significantly lower pain scores than the BG at 1, 2 and 3 hours following surgery ($p < 0.05$). Rescue analgesia was administered to 11/12 (92%) and 2/13 (15%) dogs in the BG and FG, respectively ($p < 0.05$).

Conclusion and clinical relevance Firocoxib produced better post-operative analgesia than butorphanol. Firocoxib may be used as part of a multimodal analgesia protocol but may not be effective as a sole analgesic.

Keywords analgesia, butorphanol, dog, firocoxib, ovariohysterectomy.

Introduction

Ovariohysterectomy is commonly performed in small animal veterinary practice (Hewson et al. 2006). It is considered to be a noxious and fatiguing experience that causes changes in behavior during the post-operative period, which can be relieved using opioids and nonsteroidal anti-inflammatory drugs (Fox et al. 1994, 1998, 2000; Hardie et al. 1997; Mathews et al. 2001).

Butorphanol is a kappa (KOP) agonist and mu (MOP) antagonist opioid that provides mild analgesic effects of short duration (Sawyer et al. 1991; Caulkett et al. 2003). Butorphanol and nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in North America for perioperative pain control in different surgical procedures in small animal practice (Mathews et al. 1996, 2001; Hewson et al. 2006).

NSAIDs are popular for their anti-inflammatory, analgesic, and antipyretic effects on acute and chronic pain. Some of the NSAIDs are convenient for oral and once daily administration (Lascelles et al. 2005). These drugs inhibit the cyclo-oxygenase (COX) enzyme system, which is responsible for the conversion of arachidonic acid into prostaglandins and other inflammatory mediators (Vane 1971). There are at least two COX isoforms: COX-1 and COX-2. Briefly, COX-1 is a constitutive form of the enzyme that is present in many tissues and has an important role in maintaining the integrity of the gastrointestinal (GI) mucosa, normal renal blood flow and platelet aggregation. The COX-2 isoform is also constitutively expressed in a range of tissues and organs, but it is primarily induced by damage or tissue injury. The COX-2 isoform is also responsible for the production of inducible enzymes which are converted into prostaglandin end products which are mediators of inflammation and amplify nociceptive input and transmission to the spinal cord (Fu et al. 1990; Kujubu et al. 1991). NSAIDs that have a preferential or selective COX-2 inhibition appear to have greater safety profiles and promote less severe gastrointestinal side effects than nonselective NSAIDs (Luna et al. 2007).

Firocoxib is a selective COX-2 NSAID that has been licensed for veterinary use. The drug is labeled in the United States to control pain and inflammation due to osteoarthritis, or from soft-tissue surgery in dogs. Firocoxib has an over 350-fold COX-2 selectivity in an *in vitro* canine whole blood assay and it has been shown to spare COX-1 activity *in vivo* (McCann et al. 2004). In general, coxibs are more lipophilic than many nonselective NSAIDs and can readily cross the blood–brain barrier, a property that may allow them greater systemic distribution and may facilitate inhibition of the central regulation of COX-2. These properties may be associated with shorter onset of action (Buvanendran et al. 2001, 2002). To the authors' knowledge, the post-operative analgesic effects of firocoxib have never been investigated in dogs undergoing soft-tissue surgery. The aim of this study was to compare the post-operative analgesic effects after pre-operative administration of butorphanol or firocoxib in dogs undergoing elective ovariohysterectomy.

Material and methods

Animals

Twenty-five healthy (American Society of Anesthesiologists' category I) sexually intact female domestic dogs older than 1 year of age and of various breeds were included in a randomized, prospective, blinded clinical trial. Randomization was done via coin toss. Dogs were in anestrus and underwent routine ovariohysterectomy with the owner's written consent. They were considered healthy, as judged by physical examination and values that were within the reference intervals for packed cell volume (37–54%) and plasma total protein (5.8–7.8 g dL^{-1}). When necessary, a complete blood count was performed. Any dog presenting with systemic disease, cardiac arrhythmias, pregnancy, extreme aggression or that were obese (body condition score greater than 6/9) or debilitated was excluded from the study. The study protocol was approved by the Animal Care Ethics Committee of the School of Veterinary Medicine.

Dogs were admitted to the Veterinary Hospital on the day before surgery and were placed in cages equipped with bedding, and food and water bowls. Their behavior was assessed and recorded; and the abdomen palpated to observe each animal's reaction. Dogs that were hunched-up, guarding or splinting their abdomen, aggressive and/or vocalizing during abdominal palpation were considered to be painful and were not included in this study. Food, but not water, was withheld for at least 12 hours before anesthesia.

Experimental protocol

Dogs were randomly assigned to two different groups: butorphanol group (BG) or firocoxib group (FG). Dogs were pre-medicated with 0.05 mg kg^{-1} of acepromazine (Acepran 0.2%; Lab Univet, São Paulo, SP, Brazil) intramuscularly (IM) and either 0.2 mg kg^{-1} of butorphanol (Torbugesic; Fort-Dodge, Campinas, SP, Brazil) (BG; $n = 12$) or 5 mg kg^{-1} of firocoxib (Previcox; Merial, Paulinia, SP, Brazil) (FG; $n = 13$) was administered by the IM or oral route

(PO), respectively. In the BG, acepromazine and butorphanol were mixed in the same syringe. In the FG, dogs received acepromazine and saline 0.9% (equivalent volume of butorphanol). The quadriceps muscle was used for IM injections. Although dogs were constantly observed for clinical signs of toxicity related to NSAID administration such as anorexia, diarrhea, vomiting, melena, among others, the study was not designed to investigate the safety of firocoxib in this species and this has been reported elsewhere (Steagall et al. 2007).

Approximately 30 minutes after pre-medication, a cephalic vein was catheterized, using aseptic technique, and anesthesia was induced with propofol (Propovan; Lab Cristália, Itapira, SP, Brazil) intravenously (IV) over 20–30 seconds in order to achieve moderate depth of anesthesia (eyeball rotation, absent palpebral reflex and decreased jaw tone) and until intubation with an appropriately sized, cuffed endotracheal tube could be performed. Dogs were then positioned in dorsal recumbency on a thermal blanket for instrumentation and surgery. Anesthesia was managed by a single observer (SERSL) and maintained with isoflurane (Isothane; Baxter Health Care Corporation, Guayama, Puerto Rico, USA) in oxygen via a circle rebreathing system. Eucapnia ($P_E'CO_2$ values from 35 to 45 mmHg) was maintained via intermittent positive-pressure ventilation using a volume-limited time-cycled ventilator (Conquest 2000; HB Hospitalar, São Paulo, SP, Brazil).

Pulse rate and systolic arterial blood pressure were monitored using Doppler pulse detection (Ultrasonic Doppler Model 811-B; Parks Medical Electronics, OR, USA). Body temperature was monitored with a rectal thermometer. Airway gas samples were continuously obtained from the proximal end of the endotracheal tube and analyzed with an infrared gas analyzer (AS/3; Datex-Engstrom, Helsinki, Finland) to monitor end-tidal carbon dioxide concentrations ($P_E'CO_2$) and end-tidal isoflurane concentrations ($E'ISO$). No attempt was made to compare cardiorespiratory variables or isoflurane requirements between groups during surgery. A lactated Ringer's solution was administered at 10 mL kg hour^{-1} throughout surgery. In case of hypotension, vaporizer concentrations were reduced and a fluid bolus of 60 mL kg hour^{-1} was administered.

All surgeries were performed by one experienced surgeon (BWM). Using a scalpel blade, a ventral midline incision was performed over the skin, subcutaneous tissue and the linea alba. A standard 3-clamp technique was used. The abdominal wall was closed with no greater than appositional tension using a simple continuous pattern of absorbable sutures and the skin was closed in a simple interrupted pattern. Based on the anesthetic record, surgery time (time elapsed from the first incision until placement of last suture), anesthesia time (time elapsed from injection of propofol to termination of isoflurane administration), and extubation time (time elapsed from termination of isoflurane until extubation) were recorded for each dog. Extubation was performed when the dog started coughing and/or gagging from the endotracheal tube.

Assessment of sedation and post-operative pain

The degree of pain and sedation was assessed before anesthesia (time 0) and at 1, 2, 3, 4, 6, 8 and 20 hours after the end of surgery by a single investigator (JBC), who was blinded to the analgesic treatments and experienced in the interpretation of signs of pain in dogs. Pain scores were awarded according to a dynamic and interactive visual analog scale (DIVAS). The DIVAS was derived by using 100 mm lines where no pain was scored at 0 mm and worst pain that the investigator imagined could ever come from an ovariohysterectomy at 100 mm. The investigator marked the line according to the degree of pain perceived to be experienced by the dog and the resulting length was used as a score. First, each dog was examined without being removed from her cage and without being disturbed. Then, while observing her reaction and behavior, the investigator greeted the dog by calling her name. The animal was finally approached, spoken to, and the cage door opened. The dog was then gently handled, petted, encouraged to walk and to move around. Finally, the incision site, surrounding skin and abdomen were palpated and a mark was placed on the pain DIVAS line (0–100) corresponding to the degree of pain perceived to be experienced by the animal. Sedation was also scored using the DIVAS, where fully conscious was scored as 0 mm and unconsciousness as 100 mm. Sedation assessment was based on the subjective evaluation of the dog's behavior and attitude.

Rescue analgesia

If the DIVAS pain score was ≥50 during post-operative monitoring, dogs in the BG received 0.5

mg kg^{-1} of morphine (Dimorf; Lab Cristália) IM and 5 mg kg^{-1} of firocoxib, PO while dogs in the FG received morphine (0.5 mg kg^{-1}, IM) only. Rescue analgesia was administered by an investigator who was not involved with pain scoring. This individual was asked to provide intervention analgesia as needed by the observer performing the pain scoring. After the administration of morphine, dogs were reassessed every 20 minutes in order to assure adequate analgesia. The number of dogs receiving intervention analgesia was recorded and compared among treatment groups. Data collected after rescue analgesia were not included in the statistical analysis.

Statistical analysis

Statistical analysis was performed using a statistical software package (GraphPad Prism; GraphPad Software Inc., CA, USA). Data are reported as mean ± standard deviation (SD) or median (range). Groups were compared using paired *t*-tests or Mann–Whitney *U*-test where applicable. Differences in incidence of treatment failure were analyzed using the Fisher's exact test. Significance was defined at $p < 0.05$.

Results

Breeds included in the study were crossbred ($n = 19$), Cocker Spaniel ($n = 1$), Pit bull Terrier ($n = 1$), Labrador Retriever ($n = 1$), Miniature Pinscher ($n = 1$), Miniature Poodle ($n = 1$) and Dachshund ($n = 1$). All dogs remained healthy throughout the study and recovered uneventfully after surgery.

There were significant differences between groups for anesthesia time and propofol requirements ($p < 0.05$) but not for mean body weight, surgery and extubation time (Table 1), and DIVAS sedation scores (Table 2) ($p > 0.05$). Age was not compared between groups because most animals were young adults but their age was often unknown.

Eleven animals that received butorphanol (91.7%) and two that received firocoxib (15.4%) required rescue analgesia. There was a significantly higher incidence of treatment failure in the BG when compared with the FG ($p < 0.05$) (Table 3). Dogs were considered to be comfortable and not painful after administration of rescue analgesia.

None of the dogs demonstrated any indication of pre-existing pain or sedation, and all were assigned a DIVAS pain and sedation score of 0 before surgery. Immediately after surgery, DIVAS sedation scores were increased significantly from the pre-operative scores in all groups, falling to zero by 20 hours after surgery (Table 2). The DIVAS showed that animals that received firocoxib had significantly lower pain scores than butorphanol at 1, 2 and 3 hours following surgery (Table 2) ($p < 0.05$). Data were not compared between groups at 4, 6, 8 and 20 hours because only one dog had not received rescue analgesia in the BG, and data collected after rescue analgesia were not included in the statistical analysis. At the moment of intervention analgesia administration, dogs that were administered rescue analgesia had a DIVAS pain score (median, range) of 57 (52–82).

Discussion

This study showed that dogs that received pre-operative administration of firocoxib had significantly lower DIVAS pain scores after ovariohysterectomy than animals receiving pre-operative butorphanol. Based on these findings, the results suggest that, at the doses used, firocoxib will produce superior post-operative analgesia to butorphanol in the clinical setting. This study also provides additional information that a single pre-operative dose of butorphanol does not provide sufficient analgesia.

Table 1 Mean ± SD body weight, surgery time, anesthetic time, total dose of propofol and extubation time in dogs undergoing ovariohysterectomy after intramuscular or oral administration of 0.2 mg kg^{-1} butorphanol ($n = 12$) or 5 mg kg^{-1} firocoxib ($n = 13$), respectively

Group	Body weight (kg)	Surgery time (minutes)	Anesthetic time (minutes)	Total dose of propofol (mg kg^{-1})	Extubation time (minutes)
Butorphanol	7.9 ± 5.0	10 ± 2	14 ± 6*	2.6 ± 0.6	8 ± 5
Firocoxib	11.5 ± 4.6	9 ± 3	10 ± 4	5.4 ± 1*	8 ± 4

*indicates a significant difference between groups ($p < 0.05$).

Table 2 Median (range) dynamic and interactive visual analog scale (DIVAS) pain and sedation scores of dogs undergoing ovariohysterectomy after intramuscular or oral administration of 0.2 mg kg^{-1} butorphanol (n = 12) or 5 mg kg^{-1} firocoxib (n = 13), respectively

	Post-operative assessment time (hours)						
Groups	**1**	**2**	**3**	**4**	**6**	**8**	**24**
Butorphanol							
Pain	50 (17–82)*	48 (24–61)*	57 (57–58)*	9	13	11	10
	n = 12	n = 6	n = 3	n = 1	n = 1	n = 1	n = 1
Sedation	18 (8–60)	19 (0–66)	8 (0–51)	6 (0–39)	0 (0–28)	0 (0–28)	0
	n = 12	n = 12	n = 12	n = 12	n = 12	n = 12	n = 12
Firocoxib							
Pain	20 (7–52)	17 (5–53)	18 (5–21)	15 (5–24)	17 (6–22)	15 (4–26)	15 (3–21)
	n = 13	n = 12	n = 12	n = 12	n = 12	n = 12	n = 12
Sedation	19 (5–46)	8 (0–42)	0 (0–35)	0 (0–33)	0 (0–19)	0 (0–9)	0
	n = 13	n = 13	n = 13	n = 13	n = 13	n = 13	n = 13

*indicates a significant difference between groups ($p < 0.05$).

Table 3 Number of animals receiving rescue analgesia over time in dogs undergoing ovariohysterectomy after administration of 0.2 mg kg^{-1} butorphanol (n = 12) or 5 mg kg^{-1} firocoxib (n = 13), respectively

	Number of animals receiving rescue analgesia over time (hours)							
Group	**1**	**2**	**3**	**4**	**6**	**8**	**20**	**Total**
Butorphanol	6	3	2	0	0	0	0	11/12 (91.7%)*
Firocoxib	1	1	0	0	0	0	0	2/13 (15.4%)

*indicates a significantly higher incidence of treatment failure in the BG when compared to FG ($p < 0.05$).

One could argue that a low dose of butorphanol was administered in the present study (0.2 mg kg^{-1}) and higher doses may have resulted in better and more prolonged post-operative analgesia. However, previous studies using a colonic balloon have shown that duration of visceral antinociception was not significantly different between different doses of butorphanol (0.025, 0.05, 0.1, 0.2, 0.4, and 0.8 mg kg^{-1}) (Sawyer et al. 1991). Even high doses (0.8 mg kg^{-1}) of butorphanol produced short duration of effect (23–53 minutes) (Houghton et al. 1991; Sawyer et al. 1991). Given the results of the above studies, it is unlikely that a higher dose of butorphanol would have provided better post-operative analgesia or even would have prolonged its analgesic effect in this study. The dose of 0.2 mg kg^{-1} was chosen based on previous reports in dogs undergoing ovariohysterectomy and that had received butorphanol pre-operatively (Caulkett et al. 2003).

Butorphanol has been shown to produce inferior analgesic efficacy to NSAIDs such as ketorolac, flunixin, meloxicam and etodolac in dogs undergoing different surgical procedures (Mathews et al. 1996, 2001; Caulkett et al. 2003; Inoue et al. 2006). These studies have demonstrated that, in this species, butorphanol may not provide adequate post-operative analgesia. Our study supports these findings and shows that firocoxib, a selective COX-2 inhibitor, provides better analgesia than butorphanol after elective ovariohysterectomy in dogs. It is probably not clinically practical to compare butorphanol with a long acting NSAID such as firocoxib. Indeed, repeat dosing with butorphanol might provide similar analgesia to a single dose of firocoxib but realistically, this is not applicable in most clinical situations. In addition, studies have shown that an injection of butorphanol IV at the end of surgery is not effective at controlling post-operative pain in dogs undergoing soft-tissue surgery, even shortly after administration (Mathews et al. 1996, 2001).

In a previous study, butorphanol did not provide adequate post-operative pain control in dogs that had undergone cystotomy or splenectomy (Mathews et al. 2001). In that study, 11 of 12 dogs in the butorphanol treatment group required additional analgesia. Our findings are in agreement with the

study by Mathews et al. (2001): 11 of 12 dogs required additional analgesic treatment and there was a significantly higher incidence of treatment failure in the BG when compared with the FG. Furthermore, it is not surprising that 50% and 25% of the dogs in the BG required rescue analgesia at 1 and 2 hours, respectively, if one considers the short duration of action of this opioid.

In Canada, it was estimated that 6458 spays were performed monthly in the year of 2001 without any pre-incisional or post-incisional analgesia (Hewson et al. 2006). Butorphanol was the most common pre- and post-incisional analgesic used in dogs (48.9% and 21.8%, respectively) across all surgeries (Hewson et al. 2006). The same study showed that, among veterinarians who administered analgesics, there was an overreliance on weak opioids such as butorphanol with insufficiently frequent dosing intervals. These findings are of great concern: many surgeries are still being performed without the use of analgesics in dogs, and even when an analgesic treatment is administered it is not likely to be the best choice for the patient if one considers butorphanol as a mild analgesic with short duration of action. In the authors' experience, other opioids such as morphine and hydromorphone may be preferred over butorphanol in dogs undergoing ovariohysterectomy.

Animal behavior in response to pain can be difficult to interpret after surgery but the pain DIVAS was able to distinguish differences between the BG and FG. Previous studies have indicated that DIVAS correlates with signs of pain after surgery in dogs (Lascelles et al. 1994; Shih et al. 2008). This method has been widely used and has also been correlated to objective mechanical nociceptive threshold measurements in the dog (Lascelles et al. 1997). Although numerical rating scales (NRS) may seem more sensitive for scoring post-operative pain in small animals, the DIVAS has been shown to be more reliable and easy to use by an experienced observer (Mathews 2000; Holton et al. 2001). It is considered to be a reproducible method of pain assessment in small animals. The DIVAS is subject to a wide degree of observer variation, as it does not have defined categories, but it is thought to have more sensitivity than the NRS or the simple descriptive scale (SDS) (Firth & Haldane 1999). This method is considered to be only appropriate if, as in this study, a single experienced observer is used, as there may be a high amount of variability in pain scores and large inter-observer variation (Holton et al. 2001). In this study dogs were administered rescue analgesia if DIVAS pain scores were ≥50, as indicative of moderate pain. This is an arbitrary cut-off point and there is no consensus on what score should be chosen for intervention. The present scoring systems might have been even more robustly tested by including a control group where no analgesic was administered pre-operatively but using the same rescue protocol, since, as pain scores decrease; it becomes difficult to differentiate a drug effect from the change with time. Our study was able to show statistically significant differences between the groups so the addition of a placebo group was unnecessary.

Clinical studies can be challenging due to inherent difficulties associated with subjective measurement of pain in animals. For this reason, the current investigation tried to minimize variations associated with drug protocols and subjects, and reduce experimental error. An exclusion criterion was used and all healthy female dogs were comparable in weight and stage of the reproductive cycle. Dogs were admitted on the day before surgery and surgeries were always carried out the following morning in order to limit stress related to hospitalization. Anesthesia was managed by the same anesthetist throughout the study and the anesthetic protocol did not include drugs that are considered to be analgesics. Each procedure was performed by a single experienced surgeon and this is likely to have resulted in more consistent and limited tissue trauma to the dogs, reducing the variability of the experiment, potentially causing less pain, and producing more reliable subjective measurement of pain. Finally, in order to avoid bias, the degree of post-operative pain and sedation was assessed by a single investigator who was blinded to the analgesic treatments. The present methodology aimed to increase the power of the experimental design and the ability to detect significant analgesic effects.

In clinical reports, firocoxib was highly effective and acceptable for controlling pain and inflammation associated with osteoarthritis in dogs (Hanson et al. 2006; Pollmeier et al. 2006; Ryan et al. 2006); and dogs with experimentally induced synovitis, treated with firocoxib were significantly less lame than those treated with carprofen (McCann et al. 2004). However, to the authors' knowledge, this is the first study that reports the post-operative analgesic effects of firocoxib in dogs undergoing soft-tissue surgery such as ovariohysterectomy. According to the drug's label in the United States

(http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/DrugLabels/UCM050403.pdf), two hundred fifty-eight client-owned dogs of various breeds were randomly administered firocoxib or a control (sham-dosed-pilled) for the control of post-operative pain associated with soft-tissue surgery. Surgical procedures included ovariohysterectomy, abdominal cryptorchidectomy, splenectomy, cystotomy or major external surgeries such as mastectomy or skin tumor removal. The study demonstrated that firocoxib treated dogs had significantly lower incidence of rescue medication than the control group. Our results showed that firocoxib provided good control of post-operative pain in dogs undergoing ovariohysterectomy but since two dogs required rescue analgesia within this group, firocoxib as a sole analgesic agent may not alleviate pain in all subjects and this highlights the importance of assessing each patient individually for evidence of pain. Firocoxib provided better post-operative analgesia than butorphanol but may not be the best treatment option. In clinical settings, the combination of an NSAID with an opioid is preferred since it is likely that multimodal analgesia provides better analgesic effect than a unimodal treatment (Inoue et al. 2006).

After pre-medication with acepromazine, dogs that received firocoxib (FG) required a significantly higher induction dose of propofol than dogs receiving butorphanol (BG). In agreement with the report of Geel (1991), neuroleptanalgesia reduces the required dose of propofol. It is unlikely that higher doses of propofol used in the FG affected the results of our study. In addition, anesthesia time was significantly different between groups in our study (BG: 14 ± 6 minutes; FG: 10 ± 4 minutes) and it could have been due to longer instrumentation and positioning times.

In summary, at the doses used, pre-operative firocoxib provided superior post-operative analgesia to butorphanol. Pre-operative butorphanol did not provide effective analgesia in dogs undergoing ovariohysterectomy. Two animals in the FG received rescue analgesia suggesting that firocoxib is not completely effective and consideration should be given to using it as part of a multimodal approach to pain management.

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