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ORIGINAL ARTICLE

Effect of meloxicam or robenacoxib administration timing on renal function and postoperative analgesia in cats undergoing ovariohysterectomy: A randomized, blinded, controlled clinical trial

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Abstract

We evaluated the effect of administration timing of meloxicam and robenacoxib on renal function, platelet cyclo-oxygenase and perioperative analgesia in 60 cats undergoing ovariohysterectomy, in a prospective randomized blinded controlled study. Twelve cats were randomly allocated to one subcutaneous treatment group: meloxicam (0.2 mg/kg) or robenacoxib (2 mg/kg) at admission (MA, RA), at induction (MI, RI) and robenacoxib at the end of surgery (RE). All cats received the same anaesthesia protocol. Plasma renin activity (PRA), plasma creatinine, drug concentrations and serum thromboxane (TxB_2) were measured sequentially. Anaesthesia significantly increased PRA, as activity at end of the surgery was higher than 2 h later (mean ± SD: 26.6 ± 2.8 versus 10.0 ± 3.9 ng/mL/h). PRA remained higher at 2 h post-surgery in admission groups compared to induction groups ($p = .01$). Serum TxB_2 was lower with meloxicam than robenacoxib ($p = .001$), and was lower in the MA than each robenacoxib group at catheter placement. Admission groups (16/24 from RA and MA groups) received earlier rescue analgesia than other groups ($p = .033$). In conclusion, the renin-angiotensin system was activated during anaesthesia despite cyclo-oxygenase inhibition, possibly due to hypotension or surgical stimulation. There was no effect of drug or timing on the markers of renal function.

KEYWORDS
anaesthesia, feline, non-steroidal anti-inflammatory drugs (NSAIDs), plasma renin activity, thromboxane

1 | INTRODUCTION

Postoperative inflammation and pain occur as a result of tissue damage disruption during surgery. Cyclo-oxygenase (COX) transforms arachidonic acid in cell membrane lipids into various prostanoids. After injury, COX-2 is up-regulated to produce prostaglandin(PG)E_2, a key mediator of inflammation and pain. PGE_2 facilitates the generation of nociceptive impulses from the injured tissue and amplifies

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persisting nociceptive inputs to the spinal cord, possibly leading to an increased perception of the intensity of a stimulus (hyperalgesia) (Fox, 2010).

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective analgesics for postoperative pain; they block PGE_2 production by inhibiting COX-2 (Ochroch et al., 2003). NSAIDs are potentially nephrotoxic as regulation of renal blood flow during hypotensive stress is dependent on prostaglandins produced by the housekeeping form of COX, COX-1 (Pelligand & Elliott, 2017). COX-1 and COX-2 have been postulated to generate the signal from the macula densa to renin secreting cells in cats (Pelligand et al., 2015) and therefore COX suppression could cause postoperative renal dysfunction in a surgical patient. This may result from hypoxic damage to medullary nephrons, secondary to hypotension or hypovolaemia, which may be exacerbated by the use of NSAIDs (Jones & Lee, 2008; Sear, 2005). Acute alteration of renal function is rarely documented in elective surgical procedures when NSAIDs have been administered preoperatively, presumably due to the use of perioperative supportive care (intravenous fluid administration and cardiovascular monitoring) and because the evaluation of potential renal injuries through serum creatinine is insensitive (Sear, 2005). Measuring glomerular filtration rate (GFR) is the most accurate method for estimation of renal function (Finch et al., 2018) but impractical. Other clinical biomarkers of renal function have been identified in the cat; plasma renin activity (PRA), fractional electrolyte excretion, proteinuria and enzymuria but to our knowledge have not been used to monitor the effects of NSAIDs administration during general anaesthesia (Von Hendy-Willson & Pressler, 2011).

In humans, minor increases in PRA have been documented in normotensive patients under general anaesthesia, whereas arterial hypotension at the time of general anaesthesia induced a long-acting stimulation of renin release (Witassek et al., 1980). There is a paucity of literature surrounding the effect of NSAIDs on PRA and no documented studies investigating the role of PRA in anaesthetized cats undergoing surgery. In conscious cats administered furosemide, ketoprofen administration has been shown to reduce the increase in PRA, whereas robenacoxib had no effect (Pelligand et al., 2015) suggesting that inhibition of COX-2 alone was insufficient in supressing this response. PRA would be expected to increase under general anaesthesia primarily due to a decrease in effective circulating blood volume and the role of the renin-angiotensin system (RAAS) in renal autoregulation (DiBartola, 2012; Power & Kam, 2001) However, it is unclear whether this response would be blunted by COX-1 and COX-2 inhibition. Potentially, selectivity of NSAIDs may influence PRA values intra and post-operatively.

NSAIDs, such as robenacoxib (COX-2 selective) and meloxicam (COX-2 preferential), are routinely administered pre-emptively before elective surgeries such as ovariohysterectomies (King, Roberts, et al., 2016; Speranza et al., 2015; Steagall et al., 2022). However, human clinical trials testing the benefits of pre-emptive NSAID administration yielded equivocal results (Costa et al., 2015). Relatively few veterinary studies have indicated a benefit of pre-emptive NSAIDs administration when compared to postoperative administration (Fantoni et al., 2015; Lascelles et al., 1998).

After subcutaneous administration in cats, maximum concentrations (C_{max}) of robenacoxib (2 mg/kg) and meloxicam (0.2 mg/kg) are achieved at 1 and 1.5 h, respectively. Absorption half-lives and terminal half-lives are 1.0 versus 0.55 h and 1.1 versus 25.7 h for robenacoxib and meloxicam, respectively (Lehr et al., 2010; Pelligand et al., 2016). If administered at induction, plasma concentrations may not reach C_{max} intraoperatively, so there is a rationale for giving these NSAIDs at the time of admission rather than after induction.

The aim of this study was to provide clinical evidence regarding administration timing of NSAIDs with differing COX selectivites. We evaluated the risk-benefit ratio of preoperative robenacoxib and meloxicam administration versus postoperative administration, in a population of young healthy cats, by monitoring markers of renal function, coagulation and postoperative pain.

We hypothesized that (1) mild and reversible alterations of renal function would be measured intraoperatively, regardless of the timing of NSAIDs administration; (2) robenacoxib would have less effect on renal function and coagulation than meloxicam; (3) postoperative pain scores and predicted COX-2 activity would be lower in cats receiving pre-emptive analgesia, especially if administered several hours before surgery.

2 | MATERIALS AND METHODS

The study was a randomized, blinded prospective clinical trial comparing the perioperative efficacy and the safety of two NSAIDs, meloxicam (Metacam 2 mg/mL; Boehringer Ingelheim Ltd, UK) and robenacoxib (Onsior 20 mg/mL; Novartis Animal Health, UK) administered subcutaneously at different times relative to the beginning anaesthesia. This manuscript was prepared according to the CONSORT Guidelines (Schulz et al., 2011).

2.1 | Ethical approval

The study was approved by the Royal Veterinary College Ethics and Welfare committee and was carried out under the Animal (Scientific Procedures) Act 1986 (project licence 70/7393). This study took place at the Beaumont Sainsbury Animal Hospital from September 2011 to November 2012. Incentives were free microchipping during neutering and, if the owner completed the 3-day visit, refund of the cost of the ovariohysterectomy.

2.2 | Inclusion/exclusion criteria

Cats were eligible if they were healthy based on clinical history, basic biochemistry panel (CD8+ cartridges, i-STAT 1; Abaxis, CA, USA) and physical examination. Feral or pregnant cats, cats

treated with steroids or NSAIDs in the last 7 days, and cats with evidence of renal or hepatic disease, vomiting, dehydration or sepsis were excluded.

2.3 | Randomization of treatments

Cats were randomly assigned to one of five parallel groups of equal size, to receive one of five NSAID regimens. A randomization list with block size of 5 was generated by a study nurse using the RANDBETWEEN function of Excel (Microsoft, USA). Twelve cats received either meloxicam (0.2 mg/kg subcutaneously), administered at the time of admission into the hospital (group MA) or shortly after induction of general anaesthesia (group MI), or robenacoxib (2 mg/kg subcutaneously) administered at the time of admission into the hospital (group RA), shortly after induction (group RI) or at the end of the surgery (group RE, acting as an intraoperative control group). The principal investigator (PI) (LP) and owners were blinded to treatment group. The PI left the room at three times when the NSAIDs could have been given; administration was performed by a study nurse cognizant of randomization.

2.4 | Anaesthetic protocol and monitoring

The cats were sedated with 0.02 mg/kg of acepromazine (ACP; Novartis Animal Health, UK) and 0.02 mg/kg of buprenorphine (Vetergesic, Sogeval, UK) intramuscularly. After 15 min, an intravenous (IV) catheter was placed. Anaesthesia was induced with propofol to effect (Vetofol 1.0%; Norbrook, UK). Anaesthesia was maintained with isoflurane vaporized in 100% oxygen (Isoflo, Abbott, UK) after endotracheal intubation using a Mapleson D infant T-piece breathing system. Initial oxygen flow rate was set to 500–1250 mL/kg/min and then adjusted with capnography to a reinhaled carbon dioxide (CO_2) value of 0 mm Hg. Isoflurane vaporizer dial was initially set to 2%. No halogenate monitor was available for isoflurane inspired (FIIso) and expired ($F_{E'}Iso$) concentration measurements. Routine monitoring during anaesthesia included clinical monitoring (eye position, palpebral reflex and jaw tone) and heart rate (HR), respiratory rate (*f*R) and end-tidal partial pressure of carbon dioxide ($PE'CO_2$) (V8401; Smith Medical, UK). Non-invasive blood pressure was monitored using a doppler blood pressure monitor (DOP) (Model 811-B; Parks Medical Electronics, USA) with a size 2 blood pressure cuff on the contralateral thoracic limb to the intravenous catheter. The cats were placed on a heating mat (Carbo Tech Heating Mat; Mano Medical, France). The PI anaesthetized every cat (anaesthesia diplomate, blinded to treatment allocation). Vaporizer dial was adjusted based on clinical changes (eye position rotated, palpebral reflex absent, jaw tone relaxed, as described by Schauvliege (2016)) and changes in HR, *f*R, DOP and $PE'CO_2$. Ringer's Lactate was administered IV at 10 mL/kg/h using a volumetric pump (BD Alaris GW 800 Volumetric Pump; Becton, Dickinson and Company, UK) from shortly after induction to just before extubation. If DOP < 80 mmHg, isoflurane was reduced until jaw tone became stiff. If the cat was still hypotensive, a fluid bolus of 5 mL/kg was given over 10 min. Each routine flank ovariohysterectomy (Fossum, 2013) was performed by a team composed of an experienced surgeon (DAH or NS) scrubbed in with a veterinary student. We recorded vaporizer dial, HR, *f*R, $PE'CO_2$ and DOP every 5 min and computed individual time-averaged values, as well as minimal and maximal recorded values.

2.5 | Blood and urine sample collection and handling

Up to four blood samples were collected from each cat at different time points (Table 1). Plasma sodium, potassium, chloride, ionized calcium, total CO_2, glucose, blood urea nitrogen (BUN), creatinine, haematocrit, haemoglobin and anion gap were measured with a handheld analyser (CD8+ cartridges, i-STAT 1; Abaxis, CA, USA). Serum total solids were measured with a refractometer. We assayed TxB_2, the inactive metabolite of TxA_2, to estimate actual platelet COX-1 inhibition (Bergh & Budsberg, 2005). Blood samples were left to clot in glass tubes while incubated at 37°C for 1 h in a water bath. Serum was collected after centrifugation (2000 *g* for 5 min) and stored at −80°C until analysis. TxB_2 was measured with a competitive immunoassay (ADI-900-002; Enzo Life Sciences (UK) Ltd, UK) according to the manufacturer's instructions after sample dilution. Plasma renin activity (PRA) was measured by radioimmunoassay (Gamma Coat, CA1553; DiaSorin Ltd, UK) (Syme, 2004). Blood robenacoxib and plasma meloxicam

TABLE 1 Blood and urinary sampling times for each of the groups.

Sample collected	Catheter placement	End of surgery	2 h after extubation	3-day visit
Plasma renin activity	–	Yes	Yes	–
Plasma biochemistry	Yes	–	Yes	Yes
Serum thromboxane B_2	Yes	Yes	Yes	Yes
Blood robenacoxib or plasma meloxicam	–	Yes	Yes	Yes
Urine	–	–	Yes	Yes

Note: Five groups of 12 cats were randomly allocated to receive perioperatively meloxicam at admission (MA), at induction (MI) or robenacoxib at admission (RA), at induction (RI) and at the end of surgery (RE).

concentrations were measured using validated methods, combining high performance liquid chromatography (HPLC) with ultraviolet and mass spectrometry detections for high and low concentrations, respectively (Castineiras et al., 2021; Pelligand et al., 2016). A maximum of 5 mL of blood was sampled during the day of the surgery (5% of blood volume for a 2 kg cat). Predicted percentage of COX inhibition was computed from interpolation of whole blood assay curves (Giraudel et al., 2005), using measured robenacoxib and meloxicam concentrations. As the pharmacodynamic values obtained with a whole blood assay (efficacy, potency and Hill coefficient) account for drug protein binding, *in vitro* inhibitory concentrations (μM) are comparable with *in vivo* therapeutically relevant concentrations (after conversion to ng/mL). However, when predicting COX inhibition from plasma meloxicam concentrations, a multiplying factor of 1.5 was used to convert to whole blood concentration (cat blood haematocrit averaged 35%), assuming that meloxicam does not penetrate red blood cells (Blain et al., 2002; Giraudel et al., 2005).

A maximum of two urine samples were collected from each cat (Table 1). Manual bladder emptying following induction of anaesthesia meant subsequent samples were representative of the perianaesthetic period. The first sample was collected by cystocentesis at 2 h post-extubation. The second sample was collected by the owners at home prior to the 3-day visit, using non-absorbent litter granules. Urine creatinine (Jaffé colorimetric method), urinary specific gravity (USG, measured by refractometry), protein, sodium and potassium were measured at a commercial laboratory (ILAB 600; Idexx Laboratories Ltd, UK). Urinary protein creatinine (UPC) ratio and fractional sodium and potassium excretion were calculated (King, Panteri, et al., 2016).

2.6 | Postoperative pain scoring and analgesia management

Postoperative pain was evaluated solely by the blinded PI, at a minimum of three timepoints 15, 60 and 120 min, then 4, 6 and 8 h and at the 3-day examination. Pain was assessed using visual analogue scales (DIVAS pain and VAS wound palpation) (Cambridge et al., 2000). Another dose of 0.02 mg/kg of buprenorphine was electively administered IV 6 h after premedication if the cat did not require rescue analgesia, or as early as 4 h after premedication if the cat was about to be discharged. Rescue analgesia was administered if VAS wound palpation exceeded 50%, by administering 0.02 mg/kg of buprenorphine IV ahead of the scheduled time. If patients were hospitalized overnight for analgesia concern and deemed non-responsive to buprenorphine, methadone was administered at the discretion of the on-call veterinarian. The time point that followed rescue intervention was recorded as time of rescue. At the 3-day visit, 3 scores were recorded by the PI (pain palpation score, inflammation score and mobility score, scored from 0 to 3) and from owners (activity, appetite and social interaction, scored from 0 to 3) (Table S2).

2.7 | Study outcomes

The primary outcome was the effect of NSAID and administration timing on the renin-angiotensin system (monitored by PRA) perioperatively, compared against a control group (RE) that did not receive NSAID during surgery. Sample size was computed from the effect of ketoprofen and robenacoxib on the PRA response to furosemide (Pelligand et al., 2015). We assumed the dampening of PRA stimulation by meloxicam, though COX-1 inhibition, was similar to the one ketoprofen achieved. A minimal sample size of 11 cats for each group versus the RE control group was computed for a parallel design (https://app.sampsize.org.uk/) with 80% power and a significance level of 0.05.

Secondary outcome measures were: (1) platelet TxB_2 relative to NSAID group and predicted COX-1 and COX-2 inhibition from measured concentration, (2) postoperative pain and rescue with NSAIDs groups and timing (pre-emptive versus postoperative analgesia) and (3) volatile anaesthesia requirement – additional analysis was performed to determine if timing or type of NSAID influenced the isoflurane vaporizer dial setting.

2.8 | Statistical analysis

Statistics were carried out using the software SAS, Version 9.2.2 (SAS (2008), Cary, NC, USA). p values were two-tailed with results considered significant at $p < .05$. Data relating to NSAID administration timing, anaesthesia duration, isoflurane vaporizer dial setting, $PE'CO_2$, HR, DOP and f_R were presented as medians (25th–75th percentile). TxB_2 concentration (ng/mL) and timing of rescue analgesia are mean ± standard deviation.

Variables assessed once were tested with a one-way analysis of variance (ANOVA) for the effect of the treatment group. Variables assessed multiple times were tested in a repeated measures ANOVA (RMANOVA) for the effect of treatment group, time and interaction treatment × time; the covariance structure of repeated measurements in the same subject was taken as Autoregressive AR(1). Data were log or power transformed if that improved the normality assumption. The RMANOVA was then used to compare groups in a pairwise manner. According to the 2 × 2 factorial design, some contrasts were calculated, for example all robenacoxib groups versus all meloxicam groups, or all admission versus all induction versus the control group (end of surgery) or all preoperative versus postoperative.

3 | RESULTS

Owners of 78 female cats were approached, and 60 cats were enrolled and completed the study. Cases excluded prior to the study (recruitment) are documented in Figure 1. Breeds were domestic short hair (45), domestic long hair (7), domestic medium-hair cats (2), Bengal (1), Bengal cross (1), Persian (1), Persian cross (1), Ragdoll cross (1) and Siamese cross (1). Body weight and age for each group are summarized in supplementary data files (see Table S1). There was

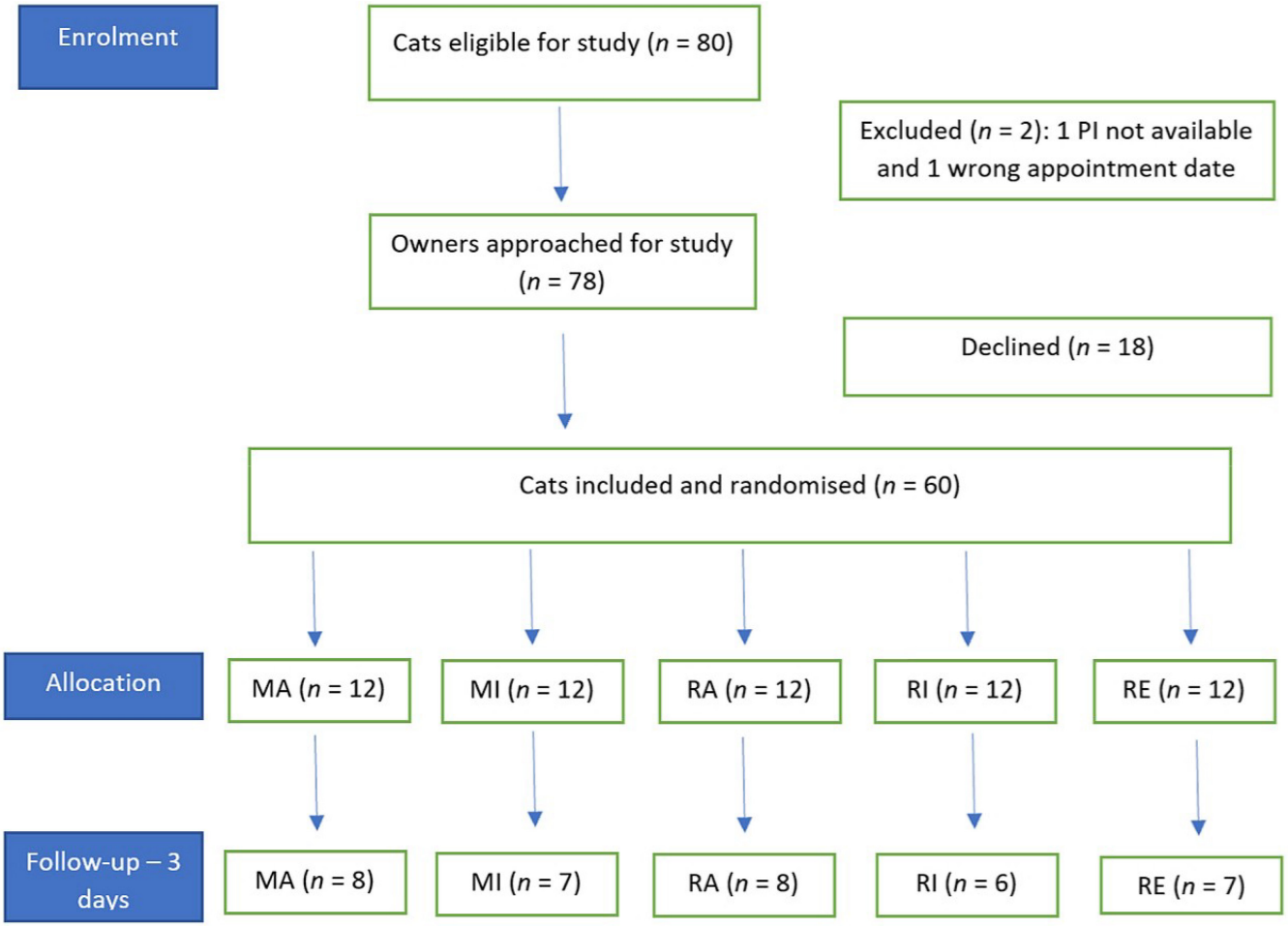

FIGURE 1 Enrolment, allocation and follow-up for cats undergoing ovariohysterectomy and their associated treatment groups, a single-centre blinded, randomized trial with a five parallel groups. Groups of 12 cats were randomly allocated to receive either robenacoxib at admission (RA), at induction (RI) or at the end of surgery (RE) or meloxicam at admission (MA) or at induction (MI). PI is the principal investigator.

no relevant difference between treatment groups for body weight or age. A total of 36 cats (60%) were seen at the 3-day visit; of these, 14 cats presented with a urine sample.

3.1 | Timing of NSAIDs administration

The admission groups (MA, RA) received meloxicam 81.5 min (median, 25–75% quantiles 67.5–113.5) and robenacoxib 112.5 min (median, 25–75% quartiles 68.8–163.7) before anaesthesia induction. Induction groups (MI and RI) received NSAIDs 5 min after induction. The RE group received robenacoxib for 57 min (median, 25–75% quartiles 49.8–63.6) after induction.

3.2 | Anaesthesia monitoring and isoflurane vaporizer setting

Median anaesthesia duration (25th–75th quartiles) for the MA group was 65 min (60–70), the RA group 59 min (45–61.25), the MI group 60 min (54.5–66.25), the RI group 70 min (68.75–76) and the RE group 55 min (48.75–60) (Figures S1–S5). The RI group had the longest mean anaesthesia duration (70.8 min) in comparison to MI, RA and RE ($p = .0318$, $p = .0016$ and $p = .0017$), followed by the MA group (mean; 65.8 min), which had longer anaesthesia duration than RA (mean; 56.5 min, $p = .0223$) and RE (56.7 min, $p = .0242$).

Median values for isoflurane vaporizer settings, average blood pressure, average $PE'CO_2$, maximal recorded blood pressure, average HR and average *f*R are presented in the Figures S1–S5. There was no significant difference between the treatment groups. Individual time-averaged vaporizer settings were not different between groups ($p = .45$); medians (25–75th quartiles) were 1.95% (1.82–2.04) for RA, 2.00% (1.85–2.07) for RI, 1.82% (1.78–2.04) for RE, 1.89% (1.73–1.95) for MA and 1.94% (1.84–2.03) for MI. Medians of individual time-averaged recorded DOP were 81.4, 87.6, 79.3, 80.2 and 82.3 mmHg for MA, MI, RA,RI and RE groups, respectively. However, minimal recorded median DOP was lowest in MA (57.3 mmHg) group compared with RA (68.5 mmHg, $p = .0060$), RI (68.2 mmHg, $p = .0039$) and RE (67.1 mmHg, $p = .0093$). As the lowest recorded DOP was only 62.7 mmHg in MA, minimal recorded DOP

was significantly lower with meloxicam than robenacoxib groups ($p = .002$). Thirty-seven cats experienced hypotension despite the high fluid infusion rate; the hypotensive episode lasted a median of 15 min (25th 75th percentile, 5–25 min). Most cats became normotensive after the first surgical incision (for two cats within 5 min and 10 cats within 10 min after the first incision). One cat that remained hypotensive for 35 min after first incision received a fluid bolus.

3.3 | Renal parameters monitoring

There was no significant difference in plasma creatinine between treatment groups at any time point (Figure 2a, Table 2). One cat in the MI group had a 0.8 mg/dL increase in serum creatinine (admission 1.4 and 2.2 mg/dL at 3-day visit), consistent with an International Renal Interest Society (IRIS) grade 1 acute kidney injury (Cowgill, 2016). Although this discovery was incidental and sub-clinical, plasma creatinine was still within the reference range (1.0–2.2 mg/dL); a subsequent visit was organized at which the cat was clinically normal and serum creatinine had returned to the pre-anaesthesia value.

Plasma renin activity (PRA) was significantly higher at extubation compared to 2 h postextubation ($p < .0001$), regardless of treatment group (Figure 2b). The PRA for the control group (RE) at extubation was not different than that of any other treatment. Compared to the MI group, the PRA for the RA group was lower at extubation ($p = .029$), then higher at 2 h postextubation ($p = .036$). At 2 h postextubation, PRA remained higher in admission groups (MA + RA) compared to induction groups (MI + RI) ($p = .01$).

Haematocrits total solids, USG, UPC and fractional sodium excretion were not significantly different between the sample time and treatment groups. However, fractional potassium excretion was higher at 3-day in RE compared to MA ($p = .0265$), MI ($p = .0470$), RA ($p = .0042$) and RI ($p = .0123$).

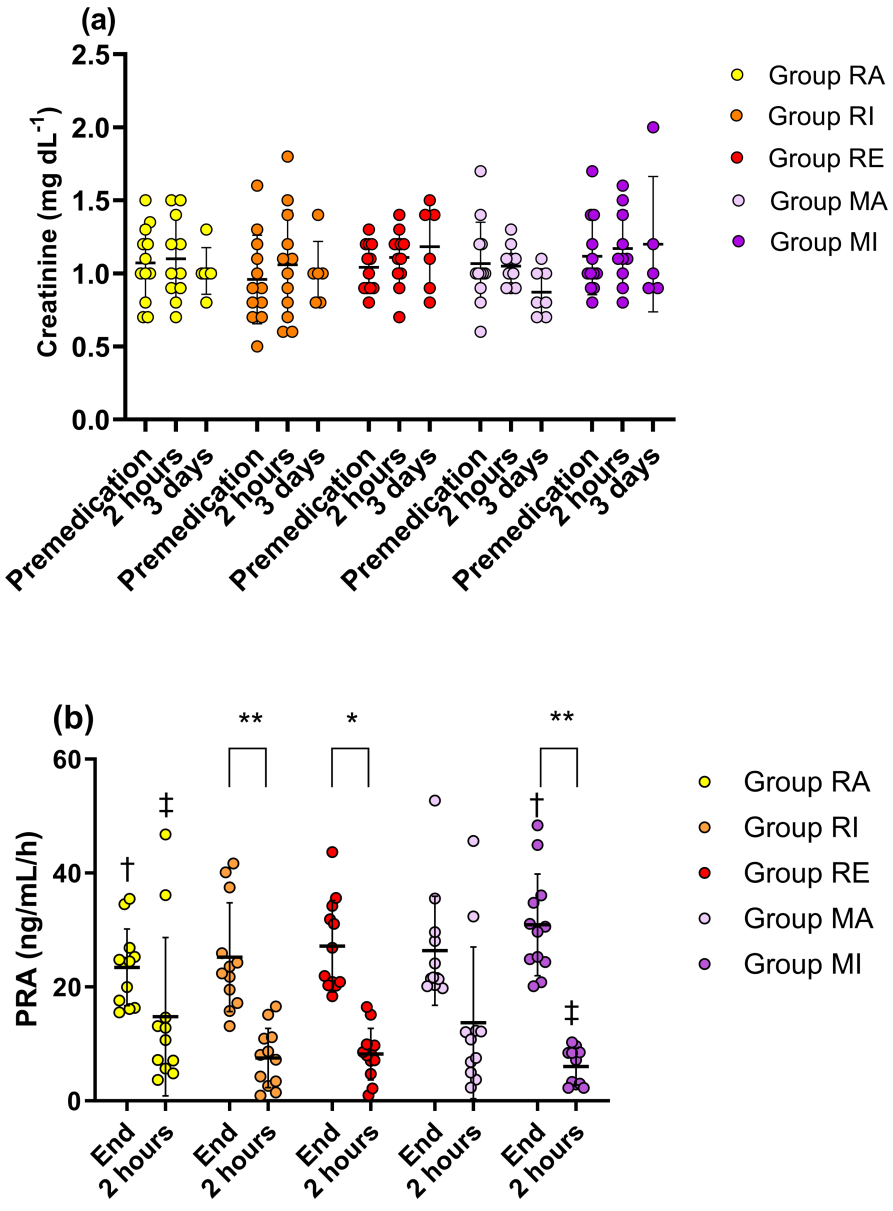

FIGURE 2 Renal parameters around surgery in groups of 12 cats randomly allocated to receive either robenacoxib at admission (RA), at induction (RI) or at the end of surgery (RE) or meloxicam at admission (MA) or at induction (MI). (a) Plasma creatinine (mg/dL) at the end of surgery, 2 h after extubation and at 3 days. Values from 10 to 12 cats mean ± standard deviation, except at the 3 days visit ($n = 5$–7). There was no significant difference between groups at any time point. (b) Plasma Renin Activity (PRA, ng/mL/h) at the time of the end of surgery and 2 h after extubation, values from 11 to 12 cats (mean ± standard deviation). $^{*}p < .001$ and $^{**}p < .0001$. PRA 2 h after extubation was lower than at the end of surgery for RI ($p < .0001$), RE ($p < .001$) and MI ($p < .0001$), but not for the groups that received NSAIDs at admission: RA ($p = .39$) and MA ($p = .09$). Compared to the MI group, the PRA for the RA group was lower at the end of surgery ($^{\dagger}p = .029$), then higher at 2 h postextubation ($^{\ddagger}p = .036$).

TABLE 2 Plasma renin activity and selected blood haematology, biochemistry and urinary measurements before induction of anaesthesia (premedication), end of surgery, 2 h after extubation or at the 3-day visit.

Variable	Reference range for each variable	Time point	Number of cases available for testing and associated mean (standard deviation) for each group									
			Group MA	*n*	Group MI	*n*	Group RA	*n*	Group RI	*n*	Group RE	*n*
Plasma renin activity (ng/mL/h)	0.28–1.02*	End of surgery	26.4 (9.6)	12	30.9[a] (8.9)	12	23.4 (6.7)	12	25.2[a] (9.5)	12	27.2[a] (8.0)	12
		2 h	13.7 (13.3)	11	6.0[b] (3.2)	11	14.8 (13.9)	11	7.5[b] (5.2)	12	8.2[b] (4.5)	12
Plasma creatinine (mg/dL)	1.0–2.2	Premedication	1.1 (0.3)	12	1.1 (0.3)	12	1.1 (0.3)	12	1.0 (0.3)	12	1.0 (0.2)	12
		2 h	1.1 (0.0)	10	1.2 (0.3)	10	1.1 (0.3)	11	1.1 (0.4)	12	1.1 (0.2)	12
		3-day	0.9 (0.2)	7	1.2 (0.5)	5	1.0 (0.2)	6	1.0 (0.2)	6	1.2 (0.3)	6
Haematocrit (%)	25–45	Premedication	30.4 (2.4)	12	30.3 (3.5)	12	31.9 (4.6)	11	29.8 (4.1)	12	31.3 (5.0)	12
		2 h	28.8 (2.7)	11	30.5 (2.6)	10	29.5 (3.4)	10	29.7 (5.1)	12	30.8 (2.8)	12
		3-day	31.7 (3.9)	7	35.0 (2.8)	6	34.3 (3.0)	6	32.3 (5.0)	6	34.0 (5.7)	6
Total solid (g/L)	60–82	Premedication	64.5 (5.4)	11	64.7 (4.7)	11	65.6 (7.4)	10	65.4 (5.9)	10	66.7 (6.0)	11
		2 h	59.8 (4.6)	10	61.1 (4.1)	10	60.6 (3.8)	10	60.8 (4.5)	9	64.1 (5.8)	11
		3-day	62.8 (5.2)	6	68.0 (5.1)	6	68.3 (4.3)	7	67.5 (6.1)	4	68.0 (2.9)	6
Urinary specific gravity	1.035–1.060	Premedication	1.042 (0.008)	9	1.042 (0.013)	10	1.048 (0.009)	8	1.035 (0.012)	9	1.043 (0.008)	9
		2 h	1.043 (0.005)	4	1.043 (0.011)	8	1.045 (0.011)	6	1.035 (0.011)	8	1.045 (0.010)	11
		3-day	1.063 (0.010)	3	1.044 (0.016)	2	1.073 (0.025)	5	1.047 (0.009)	2	1.041 (0.013)	2
Urinary protein/creatinine	<0.5	2 h	0.2 (0.0)	7	0.2 (0.1)	10	0.2 (0.1)	7	0.2 (0.1)	9	0.2 (0.0)	11
		3-day	0.2 (0.1)	3	0.1 (0.0)	2	0.1 (0.0)	5	0.1 (0.0)	3	0.2 (0.1)	3
Fractional sodium excretion (%)	<1%	2 h	0.29 (0.20)	7	0.25 (0.12)	9	0.26 (0.14)	7	0.42 (0.25)	9	0.35 (0.18)	11
		3-day	0.56 (0.06)	3	0.41	1	0.71 (0.37)	4	0.41 (0.27)	3	1.23 (0.72)	2
Fractional potassium excretion (%)	<24%	2 h	12.6 (4.8)	7	14.0 (3.3)	9	14.1 (3.3)	7	15.7 (4.5)	9	14.8 (6.1)	11
		3-day	19.4 (1.3)	3	15	1	13.4 (1.3)	4	16.0 (11.0)	3	39.8 (4.0)	2

*No reference range but median value 0.52 ng/mL/h in non-azotaemic, non-hypertensive cats (from Jepson et al., 2014).

Note: Five groups of 12 cats were randomly allocated to receive perioperatively meloxicam at admission (MA), at induction (MI) or robenacoxib at admission (RA), at induction (RI) or at the end of surgery (RE). Number of cats available for analysis at each time point between 6 and 12 (except for the 3-day visit, where numbers were too low for statistical analysis). Results are presented as mean (standard deviation). Values sharing different alphabetical superscripts for the same column differed significantly ($p < .05$).

TABLE 3 Mean ± standard deviation for serum thromboxane B_2 (TxB_2), blood robenacoxib and plasma meloxicam concentrations and predicted percentage of COX-1 and COX-2 inhibitions.

		Robenacoxib admission (RA)					Robenacoxib induction (RI)					Robenacoxib end of surgery (RE)				
	Time	*n*	Mean TxB_2 ng/mL (SD)	Average blood robenacox. (ng/mL)	%COX1 inhib.	%COX2 inhib	*n*	Mean TxB_2 ng/mL (SD)	Average blood robenacox. (ng/mL)	%COX1 inhib.	%COX2 inhib	*n*	Mean TxB_2 ng/mL (SD)	Average blood robenacox. (ng/mL)	%COX1 inhib.	%COX2 inhib
Robenacoxib	Catheter placement	12	107.8 (95.7)	Unknown			12	167.6 (138.5)	0 ($n=12$)	0	0	12	184.2 (78.6)	0 ($n=12$)	0	0
	Extubation	12	152.5 (130.0)	534 ($n=12$)	9.9	77	12	113.5 (59.7)	933 ($n=12$)	16.5	95.7	12	132.7 (81.4)	0 ($n=12$)	0	0
	2 h after extubation	11	207.9 (133.7)	103 ($n=11$)	1.9	1.4	12	194.7 (143.6)	286 ($n=11$)	5.4	29.4	12	123.1 (72.0)	413 ($n=12$)	7.8	58.7
	3-day	7	235.4 (144.7)	0[a]	0	0	7	249.5 (147.4)	0[a]	0	0	7	262.7 (150.0)	0[a]	0	0

		Meloxicam admission (MA)					Meloxicam induction (MI)				
	Time	*n*	Mean TxB_2 ng/mL (SD)	Average plasma melox. (ng/mL)	%COX1 inhib.	%COX2 inhib	*n*	Mean TxB_2 ng/mL (SD)	Average plasma melox. (ng/mL)	%COX1 inhib.	%COX2 inhib
Meloxicam	Catheter placement	12	46.8 (33.6)	Unknown			12	184.1 (197.2)	0 ($n=12$)	0	0
	Extubation	12	94.6 (96.4)	638 ($n=12$)	32.8	41.4	12	104.4 (70.6)	369 ($n=12$)	26.3	10.6
	2 h	11	82.2 (60.4)	737 ($n=11$)	34.8	53.1	12	117.7 (101.5)	775 ($n=10$)	35.4	57.2
	3-day	8	152.4 (49.6)	31 ($n=6$)	7.7	0	6	178.3 (117.3)	34 ($n=4$)	8.1	0

Note: Five groups of 12 cats were randomly allocated to receive perioperatively robenacoxib at admission (RA), at induction (RI) or at the end-of-surgery (RE) or meloxicam at admission (MA) or at induction (MI). Number of cats available for analysis at each time point between 6 and 12.

[a]A default concentration value of 0 ng/mL was assigned 3 days after robenacoxib administration (mean residence time of 1.9 h) (Pelligand et al., 2015). The % predicted COX inhibition was calculated from the interpolation of whole blood assay curves (Giraudel et al., 2005; Giraudel et al., 2009) using measured concentrations of robenacoxib in blood and meloxicam in plasma. As the pharmacodynamic values obtained with a whole blood assay (efficacy, potency and hill coefficient) account for drug protein binding, *in vitro* inhibitory concentrations (μM) are comparable with *in vivo* therapeutically relevant concentrations (after conversion in ng/mL). However, when predicting COX inhibition from plasma meloxicam concentrations, a multiplying factor of 1.5 was used to convert to whole blood concentration (cat blood haematocrit averaged 35%), assuming that meloxicam does not penetrate red blood cells (Blain et al., 2002; Giraudel et al., 2005).

3.4 | Measured COX-1 inhibition

Overall, serum TxB_2 concentrations were lower in cats given meloxicam compared to robenacoxib (RMANOVA; $p = .0010$) (Table 3). At catheter placement, TxB_2 concentration for MA (46.8 ng/mL ± 33.6) was lower than for the MI, RA, RI and RE groups (ANOVA comparison; $p = .0014$, $p = .0492$, $p = .0007$, $p < .001$) and serum TxB_2 concentrations for RA (107.8 ng/mL ± 95.7) were lower than the RE control group only ($p = .03$). At 2 h postextubation, serum TxB_2 concentration for MA was lower than RA ($p = .004$) and RI ($p = .008$) and serum TxB_2 concentration for MI was lower than RA only ($p = .03$).

3.5 | Circulating NSAIDs concentrations and predicted COX inhibition

Plasma meloxicam and blood robenacoxib concentrations at extubation, 2 h after extubation and 3 days are presented in Table 3. Although circulating concentrations of NSAIDs were not measured at catheter placement, the concentrations of meloxicam for both groups at extubation (MA: 638 ng/mL, MI: 369 ng/mL) and 2 h after extubation (MA: 737 ng/mL, MI: 775 ng/mL) were predicted to inhibit between 26% and 35% of COX-1 activity (Giraudel et al., 2005). Meloxicam maximal predicted COX-2 inhibition was 53% and 57% for MA and MI at 2 h after extubation, respectively. For the robenacoxib admission and induction groups, the concentrations at extubation (RA: 534 ng/mL, RI 933 ng/mL) and 2 h after extubation (RA: 103 ng/mL, RI 286 ng/mL) were consistent with the ones from conscious cats (Pelligand et al., 2016). These peri-operative concentrations were predicted to inhibit between 2% and 16% of COX-1 activity (Giraudel et al., 2009). Maximal predicted COX-2 inhibition was 77% and 95% for RA and RI at extubation, respectively, and 58% at 2 h after extubation in the RE group.

3.6 | Early postoperative pain assessment

Eight of 12 cats in the RA and MA groups required rescue analgesia, versus 5/12 in the RE and MI groups and 4/12 in the RI group (Figure S6). Admission groups received buprenorphine earlier (MA and RA both 2.6 h) than induction groups (MI 4.0 h, RI 4.2 h, $p = .033$), but the rescue proportion between admission and induction groups did not reach significance ($p = .08$). There was no difference in rescue rate between NSAIDs ($p = .79$).

There was no statistically significant difference in DIVAS between groups for different times or treatment groups in the postoperative period. However, VAS wound palpation at 15 min was lower for the control group (RE) compared to preoperative groups ($p = .01$), regardless of the NSAID.

Two cats (RA RE groups) were kept in the hospital overnight for additional methadone analgesia, and one cat (RI) was re-admitted the next day for overnight hospitalization (received buprenorphine and robenacoxib oral).

3.7 | Three-day examination

Re-examination at day 3 occurred in 20/36 and 14/24 cats administered robenacoxib and meloxicam, respectively (Figures S7–S9). Veterinary assessment scores, appetite and social interaction owner scores did not significantly differ between groups. Owner activity scores were higher (worse) for cats in the induction group (MI + RI) when compared with the admission group (MA + RA) ($p = .005$) and the RE control ($p = .005$).

4 | DISCUSSION

This is the first prospective, randomized blinded study investigating PRA as a specific renal marker in relation to the safety of NSAIDs administered around neutering. We found there was no effect of NSAIDs, timing or type of NSAID on the markers of renal function.

Interestingly, PRA was increased in all groups after surgery, as extubation values were significantly higher compared to 2 h thereafter. Unexpectedly, there was no difference between the PRA values in the control group (RE) and the induction/admission groups. Jepson et al. (2014) reported median PRAs of 0.52 ng/mL/h (25th–75th quartiles, 0.28–1.02) in non-azotaemic, non-hypertensive cats. In eight young healthy cats fed low-sodium dry food, Pelligand et al. (2015) measured baseline PRA at 1.89 ng/mL/h ± SD 0.82. The PRA values measured 2 h postoperatively were still higher than the baseline values of these two studies, despite the administration of IV fluid. The renin-angiotensin system must therefore have been activated during anaesthesia independently of cyclo-oxygenase inhibition, possibly due to hypotension or surgical stimulation. This has been shown in dogs and humans, in which beta-adrenoceptor blockade causes a suppression of plasma renin, indicating that renal sympathetic innervation is also involved in this response (Cambridge et al., 1992). PRA was higher at 2 h after the end of the surgery in admission groups compared with induction groups. This could be due to higher circulating levels of NSAID at this time point in the induction groups and more suppression of prostaglandins or reduced efficacy of the admission NSAID group. When comparing robenacoxib and meloxicam, there was no difference in renal markers at any time point, demonstrating they were equally safe in our population of cats undergoing routine ovariohysterectomy. This is in agreement with one study comparing meloxicam and robenacoxib for cats undergoing orthopaedic surgery, which found no difference in adverse events or biochemistry variables (Speranza et al., 2015). However, the sample size was too small to detect differences in potential uncommon adverse events.

We interpreted DOP as invasive femoral systolic pressure minus 14 mmHg following Grandy et al. (1992), hence time-averaged blood pressure appeared relatively well-maintained during anaesthesia. However, minimal Doppler pressures could act as a confounding factor influencing perioperative PRA, as minimal DOP was very low in some of the groups, in particular MA (57.3 mmHg).

Inspired isoflurane concentrations did not differ between groups. Our hypothesis that cats in the end-of-surgery (RE) group may require higher inspired isoflurane concentrations was not supported. It is possible that this study was underpowered for this comparison.

Admission groups (RA + MA) required earlier rescue analgesia than induction (RI + MI) or control (RE) groups, but the proportion of rescues between groups did not reach statistical significance. Similarly, 3-day visit activity and social interaction scores were worse for admission compared to the induction and control groups. This is an unexpected finding, as one would assume that pre-emptive NSAID several hours before noxious stimuli would give greater postoperative benefits. In the groups (MA + RA), the administration of rescue analgesia occurred 2 and 3 h post T_{max} for meloxicam and robenacoxib, respectively. With robenacoxib, the predicted COX-2 inhibition at 2 h post-extubation was consistently lower in the RA group compared to the RI and the RE group (Table 3), hence possibly contributing to the earlier rescue in the RA group compared to groups where robenacoxib was administered post-induction. With meloxicam, predicted COX-2 inhibition at extubation and 2 h thereafter did not differ between the MA and MI groups (Table 3); thus, it does not explain the superiority of administration at induction rather than at admission.

Serum TxB_2 concentrations were significantly lower in the meloxicam group, as expected, since meloxicam is only preferentially selective for COX-2, whereas robenacoxib is highly selective. According to measured circulating NSAID concentration, the predicted level of COX-1 inhibition at extubation was 26–38% with meloxicam groups and reached 34–35% 2 h thereafter, but never exceeded 16.5% in any robenacoxib group. It did not result in any haemostasis problem at the time of surgery. However, based on our data, if there is a clinical risk of haemorrhage or platelet dysfunction, the use of robenacoxib might be considered over meloxicam. A randomized study in healthy cats supports this; cats were given high-dose robenacoxib for 28 days with no change in activated partial thromboplastin clotting time (King et al., 2012), and no change in buccal mucosal bleeding time was observed in cats and dogs undergoing soft tissue or orthopaedic surgery with robenacoxib (Gruet et al., 2011, 2013; Sattasathuchana et al., 2018).

This study has some limitations. Although GFR is the gold standard for assessing renal function, this was not feasible in this setting. Symmetric dimethylarginine (SDMA) was also not available when the study started. PRA, creatinine, UPC and urinary excretion fractions were chosen as these have been shown to be more sensitive markers than creatinine alone (Finch et al., 2018). Different surgical teams could induce more or less nociceptive stimulation than other teams; however, (1) the cat allocation to treatment and surgical team was random and (2) the students were closely supervised by the veterinary surgeon, reducing possible differences in intraoperative stimulation. Students were allowed 20 min to operate, beyond which the surgeon took over the procedure. Pain recognition is not a simple task in cats due to their inability to self-report (Mathews et al., 2014). Two visual analogue pain scores were used to assess postoperative pain in this study and these have some limitations. Newer systems such as the validated Botucatu scale (Brondani et al., 2013), the Glasgow Composite Measure Pain Scale – Feline (Reid et al., 2017) or the Feline Grimace Scale (Evangelista et al., 2019) may have better assessed pain but were not available at the time of the study. Use of these in future studies could help to differentiate postoperative pain more clearly. An owner-based scoring system was used to assess pain-related behaviour at home, and this had inherent limitations. Unfortunately, some cases were lost to follow-up, meaning small numbers of cases were available for analysis, potentially risking a type 2 statistical error. Serum TxB_2 was measured as an index of COX-1 activity; lower values should result in reduced platelet activity and inhibition of primary haemostasis; thromboelastography may have provided a closer representation of *in vivo* haemostasis (Burton & Jandrey, 2020).

Controversy still exists around the timing of NSAID administration and neutering. This study was designed to replicate a clinical scenario and provide evidence to rationalize the use and timing of NSAID medication perioperatively. In this study, cats from the admission groups required earlier analgesia compared to the induction or end-of-surgery groups and renal parameters were not influenced by the timing or type of NSAID.

AUTHOR CONTRIBUTIONS

AK analysed and interpreted the data and wrote the manuscript. JNK and JE designed the study, analysed and interpreted the results and contributed to part of the manuscript. LP designed and executed the study, analysed the data and wrote the manuscript. All authors read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

JNK was previously an employee of Novartis Animal Health (now Elanco), which holds the marketing authorisation for robenacoxib. JE and LP received funding from Novartis Animal Health for a PhD on the role of cyclooxygenase in the regulation of renal function and inflammation in the cat and for the present study. The study was funded by Novartis Animal Health (grant VAP63), while LP was employed (funded by the RVC) as a clinical pharmacology fellow with clinical and teaching duties at RVC.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ETHICS STATEMENT

The study was approved by the Royal Veterinary College Ethics and Welfare committee and was carried out under the Animal (Scientific Procedures) Act 1986 (project license 70/7393).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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