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Tolfenamic acid and meloxicam both provide an adequate degree of postoperative analgesia in dogs undergoing ovariohysterectomy

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ABSTRACT: This study was aimed at comparing the postoperative analgesic effects of tolfenamic acid and meloxicam in dogs undergoing ovariohysterectomy. Ovariohysterectomy was performed in 24 female dogs. All dogs were administered pre-anaesthetic medication comprised of 0.02 mg/kg *i.m.* acepromazine, and general anaesthesia was induced with *i.v.* propofol (4–6 mg/kg) and maintained with 1.5–2.0% isoflurane. Dogs were divided into three groups (n = 8). Following induction of anaesthesia, group C received 0.05 ml/kg sterile saline *i.m.*; group T received 4 mg/kg tolfenamic acid *i.m.*; group M received 0.2 mg/kg meloxicam *s.c.* Heart rate, respiratory rate, rectal temperature, mean arterial pressure and arterial oxygen saturation of haemoglobin were monitored intraoperatively. Pain was assessed using the short form of the Glasgow composite pain scale (SF-GCPS) by two observers who were blinded to the treatment groups; pain was assessed at the time of pre-medication (baseline), and at 2, 4, 6, 8, 12 and 24 h after extubation. Rescue analgesia (0.2 mg/kg *i.m.* methadone) was administered to any dog with an SF-GCPS score of greater than or equal to six during postoperative monitoring. The pain score in group C was significantly higher compared with group T and group M at 4, 6 and 8 h, while there were no significant differences between the two treatment groups. The mean pain score in group C was also higher than that in group M at 2 h. Rescue analgesia was first administered at 4 h in group C. Rescue analgesia was required by significantly more dogs in group C (n = 8) compared with groups T (n = 0) and M (n = 1), but there was no significant difference between the two treatment groups. Thus, tolfenamic acid and meloxicam provide adequate postoperative analgesia to similar degrees over 24 h in healthy dogs undergoing ovariohysterectomy.

Keywords: postoperative analgesia; dogs; assessment; pain; SF-GCPS score

Ovariohysterectomy (OHE) is a common surgical procedure performed in small animal practice (Devitt et al. 2005; Kim et al. 2012); it is widely used in analgesic studies in dogs, as it is a surgery that produces moderate or severe postoperative pain (Slingsby et al. 2011). The pain caused by OHE can persist in the postoperative period for at least 24 h (Fox et al. 2000). Postoperative pain or surgical stress response may also cause mental suffering, muscle atrophy, weight loss, impaired respiratory function, increased blood pressure and other complications (Firth and Haldane 1999; Gaynor et al. 2002).

It is necessary to provide analgesia before surgery, as well as in the intra- and postoperative periods, for animals with pre-existing injuries. The analgesic drugs commonly used in dogs include opioid drugs, non-steroidal anti-inflammatory drugs (NSAIDs) and local anaesthetics. NSAIDs have been used in veterinary medicine to manage chronic pain states in dogs since 1997 (Fox and Johnston 1997). These drugs have anti-inflammatory, analgesic and anti-

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pyretic actions. NSAIDs function by blocking the production of prostaglandins (PGs) and thromboxane (TX) via inhibition of cyclooxygenase (COX) to generate anti-inflammatory and analgesic actions.

Meloxicam is a common NSAID used for analgesia, which preferentially inhibits cyclooxygenase-2 (COX-2) (Kay-Mugford et al. 2000). It has been approved for use in dogs in Europe, North America and Canada. Current available evidence suggests that meloxicam is safe and efficacious (Cross et al. 1997; Mathews et al. 2001; Brainard et al. 2007). Meloxicam has also been reported to produce adequate analgesia in dogs pre-medicated with acepromazine in combination with pethidine or butorphanol (Vettorato and Bacco 2011), as has been used to control acute postoperative pain in dogs undergoing splenectomy or cystotomy (Mathews et al. 2001).

Although rarely used in North America dogs to control postoperative pain in dogs, tolfenamic acid is a NSAID licensed for use in both cats and dogs in China and Europe under the tradename of Tolfedine®. Studies have shown that preoperative administration of tolfenamic acid provides effective analgesia and prevents postoperative pain in dogs (Fonda and Perini 2000; Grandemange et al. 2007). In addition, the efficacy of tolfenamic acid and meloxicam in the control of postoperative pain resulting from both orthopaedic surgery and ovariohysterectomy has also been investigated in cats (Benito-de-la-Vibora et al. 2008; Murison et al. 2010). However, there are no clinical investigations of the relative efficacies of meloxicam and tolfenamic acid in dogs. Thus, the purpose of this study was to compare the postoperative analgesic effects of these two extensively used NSAIDs.

MATERIAL AND METHODS

Animals. All procedures in this study were approved by the University Animal Care and Use Committee of Northeast Agricultural University, Harbin, China. Client-owned dogs were recruited to the study after the owners had provided written informed consent. All animals were judged to be healthy on the basis of physical examination and haematological and biochemical blood tests. Dogs were excluded if they had any gastrointestinal disease or had received any analgesic or anti-inflammatory medication in the six months prior to enrolment in this study. Before each treatment, dogs were acclimatised to the recovery room for a minimum of 24 h. Each dog had free access to water, while food was withheld for 12 h prior to induction of general anaesthesia. The baseline physiological variables, namely, heart rate (HR, beats/min), rectal temperature (RT, °C), respiratory rate (f_R, breaths/min), non-invasive mean arterial pressure (MAP, mmHg) and arterial oxygen saturation of haemoglobin (SpO_2, %) were recorded (Datex-Ohmeda S/5; Datex-Ohmeda Division Instrumentarium, Finland) for each dog.

Anaesthesia and surgical procedure. Animals were administered 0.05 mg/kg acepromazine (Acepromazine Maleate Injection; Boehringer Ingelheim Vetmedica, Missouri, USA) *i.m.* approximately 30 min before induction of anaesthesia. Dogs were randomly divided into three groups (n = 8 in each group) using a random number generator (www.numbergenerator.net/random), and received either 4 mg/kg of *i.m.* tolfenamic acid (group T; Tolfedine injection, Vetoquinol, Lure, France), 0.2 mg/kg of *s.c.* meloxicam (group M, Metacam injection; Boehringer Ingelheim), or 0.05 ml/kg of *i.m.* normal saline (group C, QiLu Pharmaceutical Co., Ltd., Shandong, China) following induction of anaesthesia.

Before *i.v.* administration of the anaesthetic induction agent, an *i.v.* cannula needle (Jinhuan Medical Products Co., Ltd., Shanghai, China) was placed through the indwelling external jugular cannula. Anaesthesia was induced in all dogs by *i.v.* administration of propofol (4–6 mg/kg, Limengxin®; Libang Management Co., Ltd., Shaanxi, China) until the anaesthetic depth was adequate for intubation with a cuffed endotracheal tube (Beter Medical Equipment Co., Ltd., Shanghai, China). Anaesthesia was maintained with 1.5–2.0% inspiratory isoflurane (RWD Life Science Co., Ltd., Guangzhou, China) mixed with 100% oxygen delivered by an agent-specific vaporiser. A semi-closed anaesthetic circle re-breathing system was used intraoperatively. The time required from administration of propofol to completion of intubation was recorded as the induction time.

Surgery began approximately 20 min after induction of anaesthesia. All surgical procedures were performed using a standard midline abdominal approach as previously described (Srithunyarat et al. 2016). All surgeries were performed by the same experienced surgeon (HGF) and assistant (YBZ)

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from the veterinary clinical teaching hospital of Northeast Agricultural University. The time-point of operation commencement was recorded as 0 min, and the time taken from the start of the incision of the abdominal wall to the closing of the abdominal wall was recorded as the surgery time. All dogs received *i.v.* Lactated Ringer's solution at 5–10 ml/kg/h intraoperatively. HR, f_R, RT, MAP, and SpO_2 were continuously monitored; data were recorded every 5 min from the time of surgery commencement for statistical analysis.

Postoperative assessment. The degree of pain was assessed after premedication (baseline) and at 2, 4, 6, 8, 12 and 24 h after extubation. The time of extubation was defined as 0 h. Once a dog was awake, it was guided to the recovery room for observation. Pain assessment was performed by two experienced graduate students (LL and WG) who were blinded to the clinical treatment of all animals. Pain scores were evaluated using the short form of the Glasgow composite pain scale (SF-GCPS) as described before (Zhang et al. 2017), in which values lower than six are considered to reflect adequate analgesia. Pain assessment was performed independently and in succession; assessors were instructed not to discuss the pain score unless they thought the animal needed rescue analgesia.

Rescue analgesia. Any dog with an SF-GCPS score equal to or greater than six during postoperative monitoring was administered *i.m.* methadone (0.2 mg/kg, Comfortan®; Dechra Veterinary Products Ltd.), and pain was reassessed after 30 min to ensure adequate analgesia. If the pain score was still higher, a second dose of methadone was administered. The numbers of dogs requiring postoperative rescue analgesia were recorded.

Laboratory data. To measure the concentration of plasma serum cortisol and PGE_2, jugular venous blood samples were collected before induction of anaesthesia, and at 0, 2, 4, 6, 8, 12 and 24 h after extubation. Samples were spun in a refrigerated centrifuge for 20 min at 3000 × *g*, and then cryopreserved at –80 °C. Plasma serum cortisol and PGE_2 levels were measured using a double antibody sandwich ELISA kit (Nanjing Jiancheng Bioengineering Institute, Jiangsu, China) according to the manufacturer's instructions. Briefly, for example, to determine the concentration of PGE_2, standards or samples were incubated with PGE_2 antibody in 96-well microtitre plates, and HRP-labelled detection antibody was then added. After incubation for 60 min at 37 °C, plates were washed according to the manufacturer's instructions. Chromogen solution was then added, and allowed to react for 10 min at 37 °C before addition of the stop solution. The optical density was recorded at 420 nm in a microplate reader (the blank well was defined as zero, Gen5 software for windows, BioTek Instruments Inc., Vermont, USA), and concentrations of PGE_2 were estimated from standard curves.

Statistical analyses. The bodyweight, age, induction time, surgery time, extubation time (the time taken from surgery completion to extubation), serum cortisol and PGE_2 concentrations are presented as the mean ± SD and were analysed using one-way repeated analysis of variance (ANOVA) with Tukey's multiple comparisons tests. A two-way ANOVA for repeated measures was used to compare the effects of each treatment group and postoperative time on HR, f_R, MAP, RT, SpO_2 and the SF-GCPS score. All the data are presented as the mean ± SD except for SF-GCPS, which is presented as the median with range. Dunnett's and Bonferroni multiple comparison post-tests were performed to identify differences within and among groups, respectively. The proportion of dogs in each treatment group requiring rescue analgesia was compared using Fisher's exact test. The results were analysed using SPSS version 19.0 (SPSS for Windows, Chicago, USA), and differences were considered significant at $P < 0.05$.

RESULTS

Twenty-six animals were recruited and two dogs were excluded due to pronounced leucocytosis. There were no significant differences between groups C, T and M in age, body weight, induction time, surgery time and extubation time (Table 1). Baseline HR was similar in the three groups; following premedication, intraoperative HR was significantly lower than baseline in all groups. There were no significant differences among the three groups in other cardiopulmonary parameters intraoperatively (Table 2).

The HR, f_R, RT and MAP of all groups at baseline, and at 0, 2, 4, 6, 8, 12 and 24 h after extubation are summarised in Table 3. Compared with baseline, the HR in group C was significantly lower at 0 h (P = 0.033), but higher at 6 h (P = 0.025). In groups T and M, the HR was higher at 12 h than at all other

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Table 1. General characteristics and selected surgical variables in each group during ovariohysterectomy. Data are presented as the mean ± SD (n = 8)

	Group C	Group T	Group M
Age (months)	12.53 ± 2.60	12.30 ± 2.58	12.13 ± 2.99
Weight (kg)	5.04 ± 0.72	4.90 ± 0.79	5.02 ± 0.52
Induction time (min)	3.46 ± 0.63	3.34 ± 0.87	3.28 ± 1.01
Surgery time (min)	36.00 ± 6.09	35.06 ± 5.47	37.28 ± 5.81
Extubation time (min)	9.33 ± 0.96	8.83 ± 2.20	8.91 ± 2.72

Following anaesthetic induction, group C received 0.05 ml/kg sterile saline *i.m.*; group T received 4 mg/kg tolfenamic acid *i.m.*; group M received 0.2 mg/kg meloxicam *s.c.*

time-points. The HR in group C was significantly higher than that of groups T and M, respectively, at 4 h (P = 0.005, P = 0.011) and 6 h (P = 0.007, P < 0.001). The RT in group C was significantly lower at 0 h and higher at 8 h than at all other time-points. There were no differences between groups or time-points in the other cardiorespiratory parameters assessed.

The pain score in all groups ranged from 1.5 to 8. In detail, in group C it was significantly higher than in groups T and M, respectively, at 2 h (P = 0.04, P = 0.001), 4 h (P < 0.001, P < 0.001), 6 h (P < 0.001, P = 0.006) and 8 h (P < 0.001, P = 0.07). There were no differences in pain scores between groups M and T during the assessment period (Figure 1). All animals in group C required rescue analgesia; a total of 11 doses of methadone were administered to eight dogs. One dog in group M required rescue analgesia at 12 h (Figure 2). Significantly more dogs in group C required rescue analgesia compared with group T (P = 0.007) and group M (P = 0.030), but there was no difference between the two treatment groups. Rescue analgesia was first administered at 4 h in group C, and most administrations were required at 6 h (n = 3 dogs) and 8 h (n = 3 dogs).

Figure 3 and Figure 4 summarise the comparative results of the laboratory data. The cortisol level in group C was significantly higher than in groups T and M, respectively, at 0 h (P = 0.002, P = 0.010), 2 h (P < 0.001, P < 0.001), 4 h (P < 0.001, P < 0.001), 6 h (P < 0.001, P < 0.001) and 12 h (P = 0.042, P = 0.003); there were no significant differences between groups T and M at any of the assessment

Table 2. Cardiopulmonary parameters in each group during ovariohysterectomy. Data are presented as the mean ± SD (n = 8)

	Group	Baseline	Time (min)					
			0	5	10	20	30	40
HR (beats/min)	C	120.4 ± 13.2^{a}	103.4 ± 12.4^{ab}	100.5 ± 10.7^{b}	98.3 ± 14.6^{b}	99.8 ± 11.4^{b}	98.3 ± 10.7^{b}	98.2 ± 10.2^{b}
	T	122.5 ± 9.8^{a}	106.4 ± 13.1^{ab}	101.8 ± 9.5^{b}	102.1 ± 10.4^{b}	100.3 ± 10.2^{b}	98.3 ± 11.4^{b}	99.2 ± 11.8^{b}
	M	124.1 ± 10.9^{a}	105.5 ± 8.6^{ab}	102.7 ± 12.6^{b}	99.4 ± 8.9^{b}	98.4 ± 12.1^{b}	98.6 ± 9.3^{b}	97.8 ± 13.4^{b}
MAP (mmHg)	C	99.8 ± 9.7	89.3 ± 8.4	90.1 ± 14.8	91.4 ± 8.3	89.8 ± 10.2	91.0 ± 7.9	88.6 ± 7.8
	T	96.3 ± 7.6	89.3 ± 10.4	90.4 ± 9.1	89.1 ± 10.6	89.0 ± 9.6	90.7 ± 10.8	90.4 ± 9.1
	M	95.5 ± 7.9	91.2 ± 9.3	92.3 ± 10.5	24.5 ± 10.3	90.9 ± 8.1	91.4 ± 7.7	89.2 ± 10.3
f_R (breaths/min)	C	24.0 ± 5.4	22.7 ± 4.2	20.0 ± 3.6	18.0 ± 4.1	18.3 ± 4.0	19.8 ± 2.3	18.0 ± 2.5
	T	24.6 ± 3.6	21.7 ± 3.2	18.5 ± 4.3	18.9 ± 3.2	18.6 ± 2.6	18.1 ± 3.3	17.9 ± 4.6
	M	23.3 ± 1.9	20.6 ± 5.2	19.1 ± 5.1	19.3 ± 4.1	17.8 ± 3.2	18.0 ± 4.8	17.9 ± 2.8
RT (°C)	C	38.7 ± 0.5	38.9 ± 0.9	38.1 ± 0.7	38.7 ± 1.9	38.4 ± 0.7	37.9 ± 1.1	38.3 ± 1.5
	T	38.4 ± 0.7	38.5 ± 1.3	38.0 ± 1.6	38.5 ± 1.0	38.2 ± 0.5	38.1 ± 0.7	37.8 ± 1.1
	M	38.5 ± 1.1	38.2 ± 1.8	38.3 ± 0.9	38.1 ± 0.8	37.8 ± 1.4	38.0 ± 0.9	37.9 ± 0.6
SpO_2 (%)	C	–	98.3 ± 0.2	98.4 ± 0.9	98.6 ± 0.4	97.8 ± 0.4	98.6 ± 0.8	98.2 ± 0.6
	T	–	98.6 ± 0.6	99.1 ± 0.3	98.7 ± 0.6	98.1 ± 0.5	98.1 ± 0.5	98.2 ± 0.2
	M	–	98.1 ± 0.3	98.8 ± 0.5	98.3 ± 1.0	98.0 ± 0.3	98.3 ± 0.4	98.3 ± 0.3

Following anaesthetic induction, group C received 0.05 ml/kg sterile saline *i.m.*; group T received 4 mg/kg tolfenamic acid *i.m.*; group M received 0.2 mg/kg meloxicam *s.c.*

HR = heart rate, MAP = mean arterial pressure, f_R = respiratory rate, RT = rectal temperature

^{a,b}Different letters represent ignificant intergroup differences (P < 0.05)

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Table 3. Cardiopulmonary parameters after extubation following ovariohysterectomy in each group. Data are presented as the mean ± SD (n = 8)

	Group	Baseline	Time (h)						
			0	2	4	6	8	12	24
HR (beats/min)	C	120.4 ± 13.2^{b}	103.3 ± 6.0^{c}	113.3 ± 13.0^{bc}	131.3 ± 8.8$^{ab*\#}$	138.0 ± 15.3$^{a*\#}$	135.0 ± 18.3^{ab}	132.3 ± 9.8^{ab}	118.0 ± 6.7^{bc}
	T	122.5 ± 9.8^{ab}	105.4 ± 13.0^{b}	108.6 ± 6.5^{b}	114.3 ± 13.1^{b}	121.6 ± 9.7^{ab}	126.2 ± 7.3^{ab}	131.0 ± 8.5^{a}	122.3 ± 11.1^{ab}
	M	124.1 ± 10.9^{ab}	100.4 ± 8.4^{b}	114.0 ± 6.7^{b}	115.8 ± 12.3^{b}	118.7 ± 7.5^{b}	129.3 ± 10.8^{ab}	130.0 ± 12.2^{a}	125.7 ± 8.5^{ab}
MAP (mmHg)	C	99.8 ± 9.7	99.5 ± 11.1	101.2 ± 11.6	106.9 ± 6.5	102.2 ± 10.5	101.8 ± 7.2	99.5 ± 10.3	97.9 ± 9.4
	T	96.3 ± 7.6	96.4 ± 10.8	97.5 ± 12.2	99.2 ± 9.5	102.0 ± 8.8	101.0 ± 10.7	99.8 ± 10.6	96.8 ± 10.2
	M	95.5 ± 7.9	96.6 ± 10.4	99.4 ± 5.8	100.5 ± 8.9	105.7 ± 11.6	102.5 ± 9.9	101.6 ± 10.4	95.4 ± 8.3
f_R (breaths/min)	C	24.0 ± 5.4	27.1 ± 2.1	26.6 ± 3.7	25.0 ± 5.0	28.8 ± 6.8	28.7 ± 9.0	29.6 ± 3.5	27.6 ± 3.2
	T	24.6 ± 3.6	25.3 ± 1.8	25.6 ± 3.6	25.0 ± 5.2	27.2 ± 6.2	27.5 ± 8.1	28.0 ± 9.5	26.7 ± 4.0
	M	23.3 ± 1.9	24.2 ± 2.3	25.3 ± 3.5	24.0 ± 4.5	26.4 ± 3.6	28.5 ± 3.5	26.3 ± 6.1	27.0 ± 5.2
RT (°C)	C	38.7 ± 0.5^{ab}	38.0 ± 1.6^{b}	39.0 ± 1.1^{ab}	39.3 ± 0.9^{ab}	39.3 ± 1.3^{ab}	39.5 ± 1.2^{a}	39.4 ± 0.8^{ab}	39.0 ± 1.1^{ab}
	T	38.4 ± 0.7	38.3 ± 0.6	38.4 ± 0.8	38.7 ± 0.6	38.2 ± 0.7	38.8 ± 0.9	39.0 ± 1.3	38.6 ± 0.8
	M	38.5 ± 1.1	38.1 ± 0.6	38.9 ± 1.0	39.0 ± 0.8	38.8 ± 1.2	39.0 ± 0.6	39.1 ± 1.1	38.6 ± 1.0

Following anaesthetic induction, group C received 0.05 ml/kg sterile saline *i.m.*; group T received 4 mg/kg tolfenamic acid *i.m.*; group M received 0.2 mg/kg meloxicam *s.c.*

HR = heart rate, MAP = mean arterial pressure, f_R = respiratory rate, RT = rectal temperature

$^{a–c}$Different letters represent significant intergroup differences during the assessment period (P < 0.05)

$^{*,\#}$Represent significant differences at the same time-point between group C and groups T and M, respectively (P < 0.05)

time-points (Figure 3). The serum PGE_2 level in group C was significantly higher than in groups T and M, respectively, at 2 h (P < 0.001, P < 0.001), 4 h (P < 0.001, P < 0.001), 6 h (P < 0.001, P < 0.001) and 8 h (P < 0.001, P < 0.001) (Figure 4); the serum PGE_2 level in group T was significantly lower than

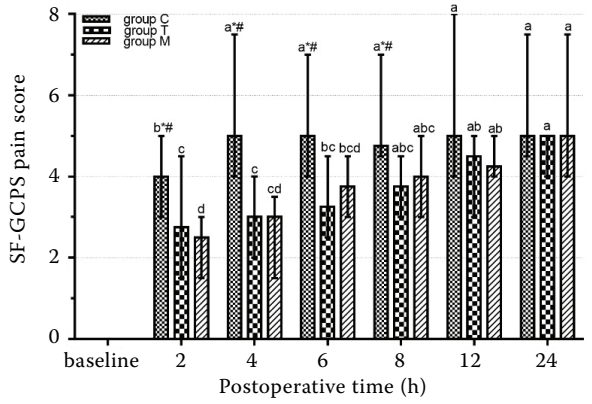

Figure 1. Short form of the Glasgow composite pain scale (SF-GCPS) scores over time after ovariohysterectomy in each group. Data are presented as the median (n = 8), with error bars indicating the range

Following anaesthetic induction, group C received 0.05 ml/kg sterile saline *i.m.*; group T received 4 mg/kg tolfenamic acid *i.m.*; group M received 0.2 mg/kg meloxicam *s.c.*

$^{a–d}$Different letters represent significant intergroup differences during the assessment period (P < 0.05)

$^{*,\#}$Represent significant differences at the same time-point between group C and groups T and M, respectively (P < 0.05)

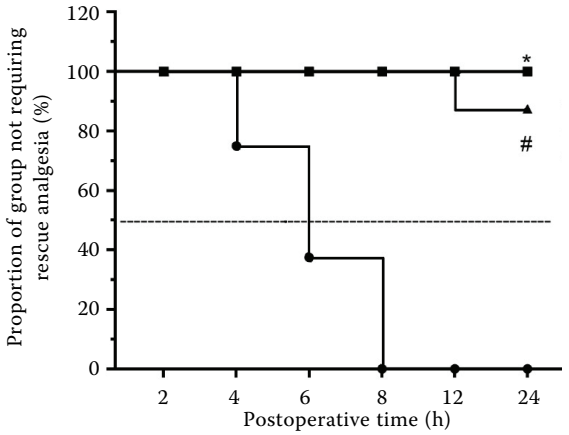

Figure 2. Proportion of each group not requiring additional rescue analgesia after ovariohysterectomy. Kaplan-Meier survival curves, in which survival is denoted by the proportion of the group not requiring rescue analgesia

Following anaesthetic induction, group C (●) received 0.05 ml/kg sterile saline *i.m.*; group T (■) received 4 mg/kg tolfenamic acid *i.m.*; group M (▲) received 0.2 mg/kg meloxicam *s.c.* The dotted line indicates 50% of the population, and intersects the survival curve at the median analgesia duration from time of premedication

$^{*,\#}$Represent significant differences between group C and groups T and M, respectively (P < 0.05)

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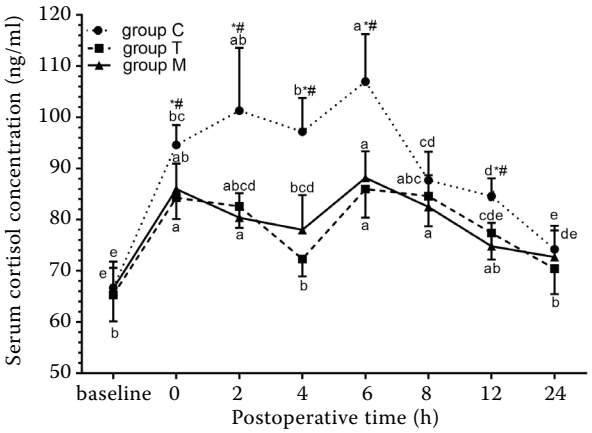

Figure 3. Serum cortisol levels over time after ovariohysterectomy in each group. Data are presented as the mean ± SD (n = 8)

Following anaesthetic induction, group C received 0.05 ml/kg sterile saline *i.m.*; group T received 4 mg/kg tolfenamic acid *i.m.*; group M received 0.2 mg/kg meloxicam *s.c.*

[a–e]Different letters represent significant differences between time-points within the same group (P < 0.05)

[*,#]Represent significant differences between group C and groups T and M, respectively, at the same time-point (P < 0.05)

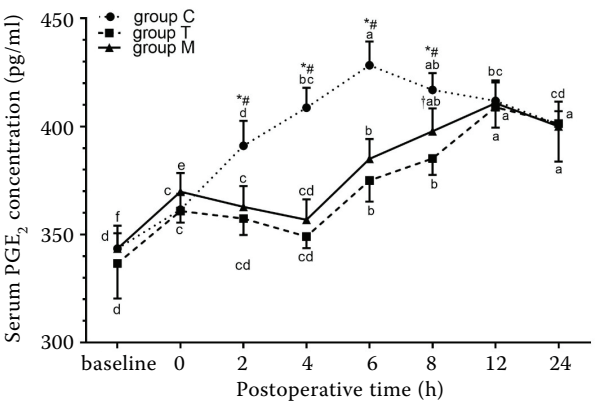

Figure 4. Serum PGE_2 levels over time after ovariohysterectomy in each group. Data are presented as the mean ± SD (n = 8)

Following anaesthetic induction, group C received 0.05 ml/kg sterile saline *i.m.*; group T received 4 mg/kg tolfenamic acid i.m.; group M received 0.2 mg/kg meloxicam *s.c.*

[a–d]Different letters represent significant differences between time-points within the same group (P < 0.05)

[*,#]Represent significant differences between group C and groups T and M, respectively (P < 0.05)

†Represents significant differences between groups T and M (P < 0.05)

in group M at 12 h (P = 0.014), but was similar in the two treatment groups at all other time-points.

DISCUSSION

The purpose of this study was to compare the postoperative analgesic efficacy of meloxicam and tolfenamic acid at their recommended dose rates. The results imply that both tolfenamic acid and meloxicam provide adequate postoperative analgesia for 24 h in healthy dogs undergoing ovariohysterectomy.

The SF-GCPS, modified by the use of the visual analogue scale, is a composite pain score measurement that can be used routinely in a clinical setting. It has been shown to be a reliable clinical tool for the longitudinal quantification of pain intensity in dogs undergoing a variety of surgeries (Kim et al. 2012). In the present study, dogs that received either 0.2 mg/kg meloxicam or 4 mg/kg tolfenamic acid had similar pain scores and did not require additional analgesia between 0 and 12 h after extubation. The pain scores in the control group were higher than those in the two treatment groups, and, therefore, the control dogs required rescue analgesia (Figure 1). Thus, a single injection of either of the analgesics successfully controlled acute postoperative pain in the dogs over this period.

A number of similar previous studies have not included a control group (Fonda and Perini 2000; Slingsby and Waterman-Pearson 2000; Nunamaker et al. 2014), while others have introduced a placebo group for follow-up studies of novel procedures (Slingsby et al. 2001; Grandemange et al. 2007). However, the use of a control group more readily permits the detection of differential effects of the analgesics under investigation. Consequently, we used a control group in our study and administered methadone as rescue analgesia to maintain appropriate animal welfare. Methadone is a full μ-opioid agonist, with an onset and duration of action similar to morphine (Selley et al. 2001). It has a short elimination half-life (1.53–4.3 h) and is well tolerated in dogs, albeit with the typical adverse effects of opioids (Kukanich and Borum 2008).

Unlike opioids, which have immediate analgesic effects, the analgesic effects of NSAIDs become evident only after 45–60 min. Peak plasma meloxicam levels are reached in dogs only 2–3 h after SC injection (Leece et al. 2005), and this drug has

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a long half-life of between 10 and 24 h. As described above, meloxicam can adequately control postoperative pain in dogs undergoing surgery for osteoarthritis or laparotomy (for splenectomy or cystotomy) (Mathews et al. 2001; Vettorato and Bacco 2011). In the present study, although one of dogs in group M did require rescue analgesia, our data indicate that adequate postoperative analgesia was achieved using meloxicam for 24 h.

Previous studies have shown that tolfenamic acid effectively controls postoperative pain for up to 24 h in dogs (Fonda and Perini 2000; Grandemange et al. 2007), and our data corroborate this duration of effective analgesia for dogs undergoing ovariohysterectomy. The pain scores and the numbers of dogs requiring rescue analgesia in group T were not significantly different from group M, indicating a similar analgesic effect of the two drugs (Figure 1), consistent with previous findings in cats (Benito-de-la-Vibora et al. 2008; Murison et al. 2010). There was a trend from 4 to 8 h for the pain scores in group T to be lower than in group M (Figure 1), although no statistically significant differences were demonstrated. This may due to the contrasting and complex metabolisms and pharmacokinetics of the two drugs (Slingsby and Waterman-Pearson 2000). For example, tolfenamic acid was shown to be 15 times more potent in inhibiting canine COX-2 than COX-1, while meloxicam was only 2.9 times more potent (Ricketts et al. 1998). In addition, tolfenamic acid not only inhibits prostaglandin synthesis, but also directly antagonises prostaglandin action at the receptor level (Paull et al. 2008).

COX-2 is expressed in the brain and spinal cord and is upregulated in response to traumatic injury and peripheral inflammation (Vanegas and Schaible 2001). As mentioned above, NSAIDs inhibit peripheral COX-2, thus reducing the synthesis of prostaglandins (such as PGE_2 and PGI_2). These prostaglandins dilate arterioles and sensitise peripheral nociceptor terminals to the actions of mediators such as histamine and bradykinin, thereby causing localised pain and hypersensitivity (Stock et al. 2001). PGE_2 can also lower the threshold for neuronal depolarisation, increasing the number of action potentials and repetitive spiking (Bergh and Budsberg 2005). In our study, serum PGE_2 levels in group M was significantly higher at 8 h than in group T, indicating that tolfenamic acid may have a stronger inhibitory effect on COX-2 or have a longer half-life than meloxicam in dogs.

The postoperative analgesic efficacy of a drug in animals is generally evaluated using both subjective and objective measurements (Kim et al. 2012), because of their inability to communicate verbally and individual variability in pain expression. Postoperative pain can result in many undesirable effects, such as decreased food intake, depression of respiratory function, cardiac dysrhythmias or progression to chronic pain (Mastrocinque and Fantoni 2003). However, some researchers consider physiological signs to be non-specific indicators of pain (Kukanich et al. 2011). Previous reports also showed no correlation between physiological indices and pain severity (Hansen et al. 1997; Holton et al. 1998). In the current study, there were no significant differences in the other physiological variables measured among the three groups, except for the HRs at 4 and 6 h in group C compared with group T and group M, respectively (Table 2). These results may suggest that physiological variables are non-specific indicators of postoperative pain.

Both acute and chronic pain, as well as surgery, can induce a stress response (Desborough 2000; Giannoudis et al. 2006). Cortisol has been used as a biomarker of stress and pain in both humans and animals (Smith et al. 1996; Hansen et al. 1997; Tennant and Hermann 2002). Our results show that plasma cortisol levels in the treatment groups were significantly lower than in the control group at 0–6 h as well as at 12 h post-extubation (Figure 3). One previous study demonstrated that ovariohysterectomy is a noxious stimulus in dogs, causing marked elevations in plasma cortisol for 6–12 h (Hansen et al. 1997), and other studies have shown that post-operative cortisol levels were higher in dogs when meloxicam was used (Tsai et al. 2013; Yilmaz et al. 2014). All these results were consistent with our data. Finally, a study that assessed the stress response of merino lambs to mulesing found that there was no difference between the effects of tolfenamic acid and meloxicam treatment on plasma cortisol; however, the responses appeared to be biphasic, with lower levels of cortisol recorded at 1–6 h in both groups (Paull et al. 2008). We did not identify a biphasic response in dogs. The differences between our results and previously published studies could have arisen due to the use of less specific methods of pain assessment and rescue analgesia; these may have affected the ability to detect minor inter-group differences. Alternatively, the differences may reflect inter-species differences.

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In conclusion, based on the use of the SF-GCPS for pain assessment, requirement for rescue analgesia and laboratory parameters, we have shown that tolfenamic acid and meloxicam provided adequate postoperative analgesia to similar degrees for 24 h in healthy dogs undergoing ovariohysterectomy.

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