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Analgesic efficacy of meloxicam with or without a buprenorphine patch in cats after ovariohysterectomy

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ABSTRACT: The purpose of this prospective double blind clinical study was to evaluate the analgesic efficacy of meloxicam with/without a buprenorphine patch for pain management after ovariohysterectomy in cats. Cats were randomly divided into two groups: ten cats were treated with meloxicam *s.c.* after ovariohysterectomy (Group A), and eight cats were treated with *s.c.* meloxicam and a 20 μg/h buprenorphine transdermal patch (Group B). For patch treatment, the cat's hair was clipped on the left side in the thoracic area. Pain scores were assessed at 0.5, 1, 2, 4, 6, 8, 24 and 30 h post-ovariohysterectomy extubation. To evaluate postoperative pain, 4A-VET pain scale and visual analogue scale pain scores were used. In addition, blood was collected from all cats to determine the cortisol levels at –2 h and at 0.5, 4, 6 and 24 h after extubation. The 4A-VET scores for Group B were significantly lower at 1, 4, 6, 8, 24 and 30 h than the scores for Group A. The visual analogue scale pain scores for Group B were significantly lower at 4, 6, 24 and 30 h than the scores for Group A. Serum cortisol concentrations were not significantly different between Groups A and B at any of the measured intervals. There was a significant positive correlation between postoperative visual analogue scale and 4A-VET pain scores in both groups. Our results should be subject to careful interpretation as the study was limited by its small sample size and by observer subjectivity.

Keywords: cat; transdermal route; postoperative pain; 4A-VET pain scale; visual analogue scale; cortisol

Pain management has become a routine procedure following surgery in veterinary medicine (Mathews et al. 2014; Bortolami and Love 2015; Merola and Mills 2015). However, clinicians may be negligent of the management of pain in cats as the detection of pain in this species is regarded as difficult by some clinicians (Watson et al. 1996; Capner et al. 1999). Ovariohysterectomy (OHE) is the most common surgery in cats, and a survey of UK veterinarians to determine their opinion about pain and perioperative analgesia showed that 957 of the 958 (99.9%) veterinarians indicated that cats feel pain after OHE (Capner et al. 1999). However, only 249 (26%) of those veterinarians prescribed perioperative analgesia for cat patients after OHE. Another study in Australia reported that only 6% of the respondents said they used pain management in cats undergoing OHE (Watson et al. 1996).

Buprenorphine is a highly lipophilic, potent, semisynthetic, partial mu-receptor opioid agonist (Mathews et al. 2014; Steagall et al. 2014; Bortolami and Love 2015; Merola and Mills 2015) that has been authorised for use in cats in the USA and Europe. Previous buprenorphine research has suggested that it has a delayed onset of action and long-acting analgesic properties that provide for moderate analgesia with few adverse effects (Sarrau et al. 2007; Steagall et al. 2014). Clinical studies in cats administered buprenorphine have shown it to be an effective analgesic when used after various surgical procedures including OHE, onychectomy and orthopaedic surgery (Mollenhoff et al. 2005; Curcio et al. 2006; Giordano et al. 2010; Moll et al. 2011; Staffieri et al. 2013; Steagall et al. 2014; Bortolami and Love 2015). Various administration routes of buprenorphine have been described in experimental studies (Johnson et al. 2007; Murrell et al. 2007; Giordano et al. 2010; Bortolami et al. 2012). Intramuscular (*i.m.*) and intravenous (*i.v.*) injections can be difficult in cats, which have fierce

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and/or sensitive characteristics; therefore, studies of alternative routes of drug administration are needed when attempting to control pain in cats. The oral transmucosal (OTM) and transdermal routes can be used in cats because they are simple, non-invasive, and pain-free. The pharmacokinetic and thermal antinociceptive effects of buprenorphine administered via the OTM route in cats have been investigated (Robertson et al. 2005; Steagall et al. 2007). Robertson et al. (2005) reported that the thermal antinociceptive effects of buprenorphine via the OTM route had an onset of action within 30 min, a peak effect at 90 min and a 6-h duration of action. The median bioavailability of buprenorphine after OTM dosing was 116.3% (Robertson et al. 2005). However, other studies have reported that *i.v.* and *i.m.* injections of buprenorphine provide better postoperative analgesia than that provided by OTM application of the drug, and buprenorphine provided less analgesia than an α-2 agonist (Gassel et al. 2005; Giordano et al. 2010).

The pharmacokinetics and thermal antinociceptive effects of buprenorphine after a transdermal dose of 35 μg/h were documented by Murrell et al. (2007). The pharmacokinetic results showed that the mean peak plasma buprenorphine concentration was 10 (0.81) ng/ml. The transdermal route did not produce a significant change in thermal antinociceptive effects (Murrell et al. 2007). However, clinical pain behaviour after surgery was not assessed in this study. Recent studies on pain in cats have focused on assessing behavioural responses. To the best of our knowledge, determination of the clinical efficacy of transdermal administration of buprenorphine for postoperative pain management after OHE in cats has not been reported.

Multimodal pain control may be used to provide better pain management in humans and in veterinary medicine. Currently, opioid drugs and α-2 agonists are used for postoperative pain management in cats. Such treatments have many advantages including good sedation, good analgesia and lower dose requirements of either opioid drug or α-2 agonist due to synergistic effects (Slingsby et al. 2010; Mathews et al. 2014; Steagall et al. 2014; Bortolami and Love 2015; Merola and Mills 2015; Wilson and Pascoe 2016). However, the effects of a combination of a buprenorphine transdermal patch with meloxicam administered via subcutaneous (*s.c.*) injection on postoperative pain in cats have not been previously studied.

The purpose of this study was to evaluate the clinical efficacy of *s.c.* meloxicam alone or *s.c.* meloxicam with a 20 μg/h buprenorphine transdermal patch on postoperative pain following OHE in cats. In addition, we assessed the correlation of 4A-VET pain scale scores with visual analogue scale (VAS) pain scores and the correlation of serum cortisol concentrations with 4A-VET or VAS scores. We hypothesised that combining *s.c.* meloxicam with a 20 μg/h buprenorphine transdermal patch would provide better postoperative analgesia than *s.c.* meloxicam alone.

MATERIAL AND METHODS

Animals. Eighteen female domestic shorthair cats (age, 8.9 ± 0.5 months and weight, 2.8 ± 0.36 kg) were included in this study. After obtaining the owners' written consent, the animals were scheduled for routine OHE performed via a ventral midline approach in the Animal Medical Center of Chonbuk National University. Cats underwent physical examination to ensure the absence of other diseases. The complete blood counts and platelet counts were determined by the use of an automated cell counter. Serum biochemical analyses included blood urea nitrogen, creatinine, alanine transaminase, alkaline phosphatase, γ-glutamyltransferase, total protein, albumin and globulin. The cats were hospitalised for 24 h prior to surgery. During that time, they were placed in individual cages without food, but water was provided for 12 h. The care and use of the animals reported in this study were approved by the Institutional Animal Care and Use Committee of Chonbuk National University.

Study groups. In this prospective double-blind study, the cats were randomly assigned to two groups using a computer software program (Microsoft Excel, Microsoft, USA). All cats were administered meloxicam (Metacam®, Boehringer Ingelheim Vetmedica, St Joseph, USA) 10 minutes after OHE. Ten cats were treated with 0.3 mg/kg *s.c.* meloxicam (Group A), and eight cats were treated with 0.3 mg/kg *s.c.* meloxicam and a 20 μg/h buprenorphine transdermal patch (Norspan®, LST Lohmann Therapie-Systeme AG, Andernach, Germany) (Group B). Prior to patch application, the cat's hair was clipped on the left side of the thorax. The 20 μg/h buprenorphine patch was applied to the shaved left thoracic area 12 h before

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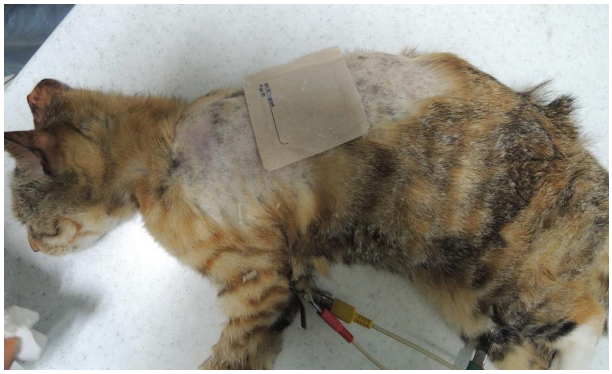

Figure 1. A 20 µg/h buprenorphine transdermal patch was applied to the left thorax 12 hours prior to ovariohysterectomy

OHE and remained in place for 72 h (Figure 1). The thoracic area in all cats was then wrapped using self-adherent wrap (3M Coban™; 3M Health Care, St. Paul, USA) to lessen the cat's awareness of the buprenorphine transdermal patch.

Anaesthesia and surgical procedures. Thirty minutes before the start of OHE, the cats received 20 mg/kg *i.m.* cephalexin (Methilexin Inj®; Union Korea Pharm., Seoul, Republic of Korea) for prophylaxis. Further, the presence of increased heart rate was assessed for the 4A-VET pain scale. The cats were premedicated with an *s.c.* injection of medetomidine (20 µg/kg *i.v.*; Domitor®, Pfizer, New York, USA). Anaesthesia was induced with 3 mg/kg *i.v.* alfaxalone (Alfaxan®; Jurox, Rutherford, Australia). After intubation, general anaesthesia was maintained with isoflurane (Ifran LIQ®, Hana Pharm., Seoul, Republic of Korea) in oxygen and air (FiO2 60%). All surgical procedures were performed by one senior surgeon (S.Y. Heo). For surgery, the patient was positioned in dorsal recumbency, which was followed by median celiotomy performed through a 3–4-cm-long skin and linea alba incision. After the ovaries were exteriorised from the peritoneal cavity, they were ligated using a three-clamp technique. A suture (3-0 polydioxanone) was then placed to include the uterine artery and vein in order to ligate the uterine body. Upon completion, the surgical incision was routinely closed in layers. Durations of surgery (time elapsed from the first incision until placement of the last suture) and anaesthesia (time elapsed from the induction to the discontinuation of isoflurane) were recorded for each cat.

Postoperative pain evaluation. Pain scores were assessed at 0.5, 1, 2, 4, 6, 8, 24 and 30 h after post-OHE extubation. The assessment of pain was performed by a single observer who was unaware of the treatment group in which the subject had been placed. Both 4A-VET pain scale and VAS pain scores were used for postoperative pain evaluation. The 4A-VET pain scores were based on subjective pain evaluation, clinical parameters and behavioural criteria (Table 1). Total scores obtained

Table 1. 4A-vet pain scores in cats

Criteria	The list of assessment	Scores
Subjective pain score (0–3)	from no pain to severe pain	
General attitude	modification of respiration	
	vaulted back	
	antalgic posture	
	abnormally agitated or depressed	
	loss of grooming	
	look at or lick the operated area	
	urinate or defecate on itself	
	loss of appetite	
Interactive demeanor	if none are present	0
	if one is present	1
	if one to four are present	2
	if more than four are present	3
Heart rate	attentive to cares and human voice	0
	timid response to cares	1
	no response to cares	2
	aggressive response	3
Reaction to manipulation of surgical area	increase from initial value < 10%	0
	increase of 11–30%	1
	increase of 31–50%	2
	increase > 50%	3
Intensity of this reaction	no perceptible reaction after four manipulations	0
	perceptible reaction after the fourth manipulation	1
	perceptible reaction at the second or third manipulation	2
	perceptible reaction at the first manipulation	3
Global pain score (1–18)	no reaction	0
	try to escape	1
	groan, turn its head	2
	try to bite	3
	weak pain	1–5
	moderate pain	6–10
	severe pain	11–18

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from the 4A-VET pain scale ranged from 0 to 18 with higher values indicating higher pain intensity (Sarrau et al. 2007; Guillot et al. 2011; Gauthier et al. 2014). For VAS pain scores (Figure 2), the degree of pain was assessed along a 100-mm line with 0 mm indicating no sign of pain and 100 mm indicating the worst possible pain (Mathews et al. 2014; Bortolami and Love 2015).

Cortisol assays. Blood samples from all cats were collected from the jugular vein in heparin tubes and were used to determine the cortisol levels at –2 h and at 0.5, 4, 6 and 24 h after extubation. The blood samples were centrifuged to remove cellular components and permit the collection of serum. Sera were stored in a deep freezer at –70 °C. Serum cortisol concentrations were measured using a chemiluminescent immunoassay method (IDEXX Reference Laboratories, Seongnam, Republic of Korea).

Statistical analysis. The ages, weights, complete blood counts and serum biochemical analyses, duration of surgery and anaesthesia, pain scores (4A-VET pain scale and VAS) and cortisol levels were plotted as histograms. Data that were normally distributed were compared using the unpaired *t*-test, and results are reported as the mean ± standard deviation. Data that were not normally distributed were compared using the Mann-Whitney *U*-test, and results are reported as median (range). Pearson correlation coefficients were calculated to evaluate the relationships between the 4A-VET pain scale and VAS scores obtained at 0.5, 1, 2, 4, 6, 8, 24 and 30 h after post-OHE extubation. Statistical tests were performed using a statistical software program (PASW® Statistics 18, SPSS, Chicago, USA). A P-value < 0.05 was considered significant for all statistical test results.

RESULTS

All cats underwent OHE without any surgical complications, and all procedures were uneventful. Preoperative complete blood counts and serum biochemical analyses of the cats were not significantly different between Groups A and B. There were no differences in duration time (min) of anaesthesia (Group A [83 ± 16]; Group B [81 ± 11] and surgery (Group A [40 ± 10]; Group B [38 ± 11] between Groups A and B. The 4A-VET pain scores for cats receiving *s.c.* meloxicam and a 20 µg/h buprenorphine transdermal patch (Group B) were significantly lower at 1, 4, 6, 8, 24 and 30 h post-extubation than scores assigned to cats receiving *s.c.* meloxicam only (Group A) (Figure 3). The VAS pain scores for Group B cats were significantly lower at 4, 6, 24 and 30 h post-extubation than scores assigned to Group A cats (Figure 4). Serum cortisol concentrations were not significantly different between Groups A and B during the period under observation. Serum cortisol concentrations were highest in Groups A and B at 2 h post-extubation. The serum cortisol reference range of 0.3–8.8 µg/dl was not exceeded at –2, 2, 24 and 30 h in Group B cats, but at 2 h post-extubation the mean serum cortisol concentration in Group A cats was higher than the upper reference limit (Figure 5).

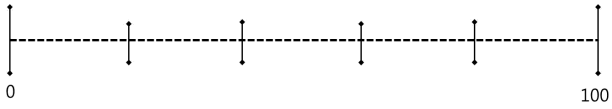

Figure 2. Visual analogue scale pain scores

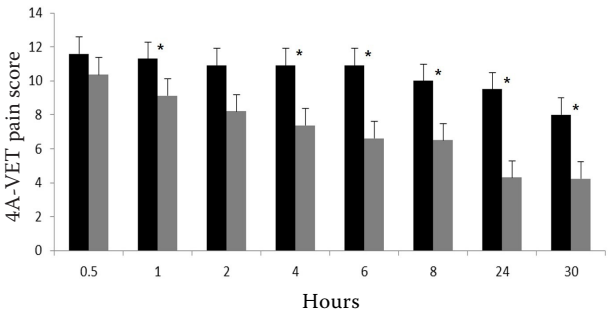

Figure 3. 4A-VET pain scores at 0.5, 1, 2, 4, 6, 8, 24 and 30 hours after surgery

*Significant difference (P < 0.05) between Groups A (■) and B (■)

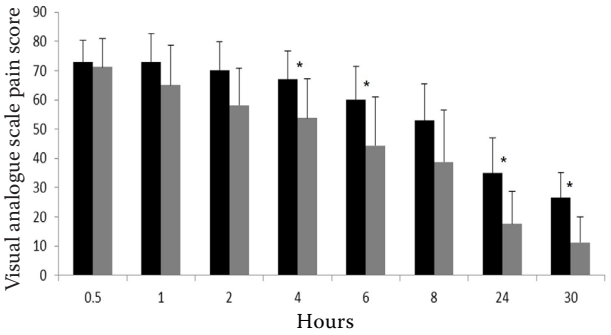

Figure 4. Visual analogue scale pain scores at 0.5, 1, 2, 4, 6, 8, 24 and 30 hours after surgery.

*Significant difference (P < 0.05) between Groups A (■) and B (■)

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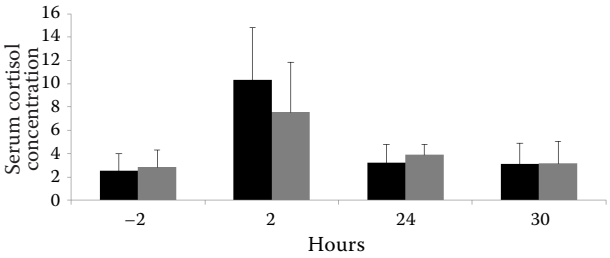

Figure 5. Serum cortisol concentration at –2 hours and at 2, 24 and 30 hours after surgery. Differences were not statistically significant
Groups A (■) and B (■)

The 4A-VET and VAS pain scores in Group A were moderately positively correlated (r = 0.593), and the correlation coefficient was significantly different from zero (P < 0.001) (Figure 6). In Group B, meanwhile, there was a highly positive correlation (r = 0.738) between 4A-VET and VAS pain scores, and the correlation coefficient was significantly different from zero (P < 0.001) (Figure 7).

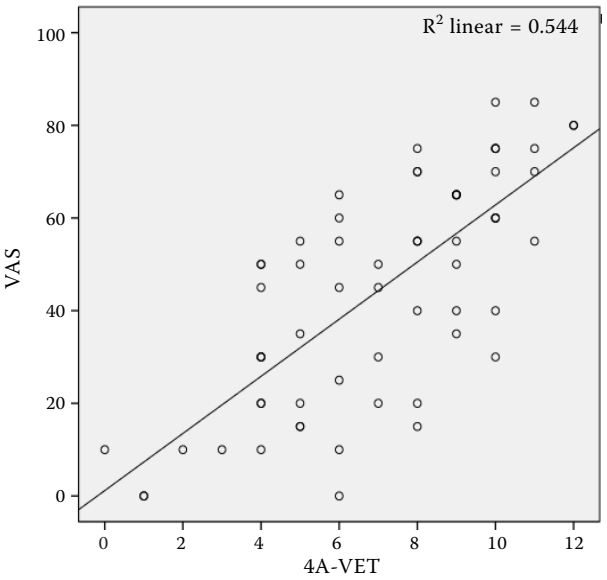

Figure 7. Correlation between visual analogue scale pain scores and 4A-VET pain scale obtained 0 to 30 hours after ovariohysterectomy in eight cats treated with a 20 µg/h buprenorphine transdermal patch and meloxicam (Group B)

DISCUSSION

The combined use of a 20 µg/h buprenorphine transdermal patch along with meloxicam (*s.c.*, 0.3 mg/kg) resulted in significantly lower 4A-VET and VAS pain scores than those from *s.c.* meloxicam alone both during OHE and at 4 h post-OHE, except for the VAS scores at 8 h post-OHE. Although a previous study (Murrell et al. 2007) showed that a 35 µg/h buprenorphine transdermal patch did not produce a significant change in thermal thresholds in six cats, the results of our study indicate that a 20 µg/h buprenorphine transdermal patch along with *s.c.* meloxicam can decrease the postoperative pain level in cats after OHE. Thermal threshold testing has been used to assess the antinociceptive effects of analgesic drugs in cats (Steagall et al. 2014; Bortolami and Love 2015), and the report by Murrell et al. (2007) used thermal threshold testing to assess the antinociceptive effect. However, their study has limitations, including no evaluation of postoperative pain and a small sample size. Furthermore, the thermal threshold testing did not evaluate the emotional components of pain.

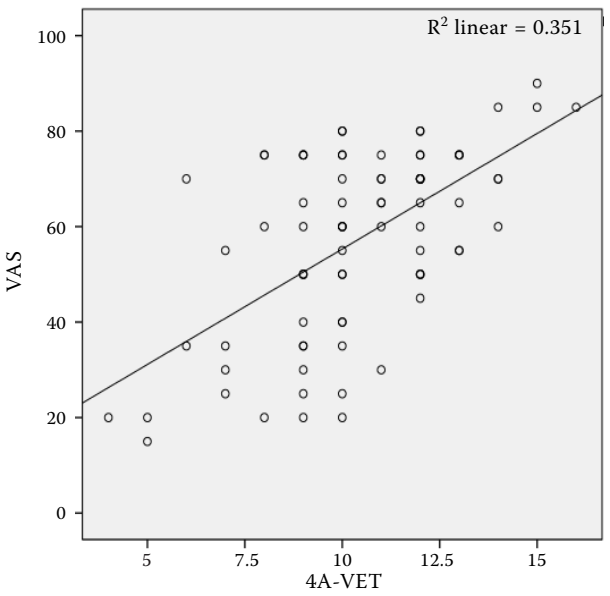

Figure 6. Correlation between visual analogue scale pain scores and 4A-VET pain scale obtained 0 to 30 hours after ovariohysterectomy in ten cats treated with meloxicam (Group A)

Pain assessment in cats is challenging as cats have less obvious expressions of emotion than dogs, and, in general, because animals are unable to verbalise unambiguously the degree of pain (Mathews et al. 2014; Steagall et al. 2014; Bortolami and Love 2015; Merola and Mills 2015). VAS pain scores have been widely used for pain assessment in dogs and cats (Mathews et al. 2014; Bortolami and Love 2015), but VAS pain scores are subjectively assessed based on a pain degree of 0 being 'no pain' and 100 being

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'worst possible pain' (Cambridge et al. 2000). In the present study, it is possible the VAS scores were unable to accurately reflect differences in pain levels because the sample size was small or the observers were biased. Grint et al. (2006) compared the midline incision and flank incision to assess the postoperative pain level in 66 cats following OHE. They reported that VAS pain scores were similar between the two surgical approaches; however, VAS pain scores related to wound tenderness were significantly higher in the flank incision approach. Recent studies using interactive behaviour scoring approaches may provide more reliable assessments of pain, and interactive approaches are likely to be more useful than biochemical markers, such as serum cortisol, in clinical practice (Grint et al. 2006; Gauthier et al. 2014).

In our study, we attempted to assess the influence of the buprenorphine transdermal patch on postoperative pain in cats following OHE using the 4A-VET and VAS pain score scales. 4A-VET pain scores are based on pain-related subject behaviour and may be more useful for accurate pain assessment than scores used in previous studies. The 4A-VET pain scoring approach combines evaluations of postoperative psychomotor changes, an objective score of physiologic and behavioural variables including reactions to palpation of the wound area (Guillot et al. 2011; Gauthier et al. 2014). In this study, 4A-VET and VAS pain score results showed significant positive correlations in both treatment groups. In contrast, a previous study using VAS and an interactive VAS pain scoring approach, which assessed pain after palpation of the surgery site (Cambridge et al. 2000), revealed different results (Gassel et al. 2005). The VAS and interactive VAS results showed poor correlation in all treatment groups. Although our study indicates that it is possible to use both 4A-VET and VAS pain scoring approaches for postoperative pain assessment in the same patient, care is needed in interpreting pain scores based on pain-related behaviours and VAS because there is no validated pain scoring system for cats. In addition, intraobserver variation can be minimised when the observer is familiarised with the used pain scoring system prior to pain assessment.

Serum cortisol concentrations are measured as an indicator of pain in many species (Anil et al. 2002). In the present study, serum cortisol concentrations after OHE were within the normal range in the group treated with *s.c.* meloxicam and a buprenorphine transdermal patch; however, the *s.c.* meloxicam only group exceeded the normal serum cortisol range at 2 h post-OHE. Regardless, there were no significant differences in serum cortisol concentrations between the two groups. A study of Tobias et al. (2006) comparing the efficacy of four types of analgesia in 52 cats following OHE used serum cortisol concentrations and VAS and interactive VAS scores to determine the degree of postoperative pain (Tobias et al. 2006). In that study, the group receiving carprofen exhibited significant changes in cortisol concentrations: levels were higher than baseline 1 h after surgery and lower than baseline at 24 h after surgery. However, there were no statistically significant differences detected in other treatment groups or at other times. Biochemical markers, such as serum cortisol, can be altered by stress and other factors more readily in cats than other species; thus, it is difficult to use serum cortisol concentrations as a quantitative metric of pain in cats (Mathews et al. 2014; Bortolami and Love 2015). In the present study, cats receiving *s.c.* meloxicam only had significantly higher pain scores than those receiving *s.c.* meloxicam and a buprenorphine transdermal patch. Both opioids and non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to alleviate postoperative pain in cats (Bortolami and Love 2015). In addition, a combination of an opioid and an NSAID has been shown to be superior to treatment with either drug type alone, providing there is an earlier peak effect of the opioid followed by a longer duration of analgesia from the NSAID (Mathews et al. 2014; Bortolami and Love 2015; Merola and Mills 2015).

Opioids delivered by a transdermal patch were originally used for postoperative pain and chronic cancer pain management in human subjects. In veterinary medicine, the fentanyl patch is commonly used for pain management (Mathews et al. 2014; Bortolami and Love 2015; Merola and Mills 2015). However, buprenorphine transdermal patches have recently been used for pain management in dogs and cats. In the USA and Europe, the buprenorphine patch is available in three sizes designed to release buprenorphine into circulation at rates of 35, 52.5 or 70 μg/h (Moll et al. 2011). In contrast, there are 5, 10 and 20 μg/h buprenorphine transdermal patches available in Korea. Although the optimum rate of buprenorphine release from a transdermal patch into circulation is unknown for the cat, 0.01–0.02 mg/kg buprenorphine given *i.v.*

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or *i.m.* has shown a thermal antinociceptive effect lasting from 0.5 to 12 h in experimental studies (Robertson et al. 2005). A study reported by Moll et al. (2011) compared results from a 70 µg/h buprenorphine transdermal patch with those from 0.02 mg/kg *s.c.* buprenorphine in 24 dogs (mean weight 12.67 ± 1.58 kg) undergoing OHE. The results indicated that the analgesia produced by the 70 µg/h buprenorphine transdermal patch was similar to that of the 0.02 mg/kg *s.c.* administration. In this study, we used a 20 µg/h buprenorphine transdermal patch in cats (mean weight 2.8 ± 0.36 kg) and the results indicate that this was an effective multimodal analgesic strategy. Based on the results of the present study, a buprenorphine transdermal patch with meloxicam can be applied to cats for the reduction of postoperative pain.

In conclusion, our results show that post-OHE pain in cats can be reduced by the use of a postoperative analgesic and that a buprenorphine transdermal patch can be used for postoperative pain management in cats undergoing a surgical procedure. We observed significant positive correlations between VAS and 4A-VET pain scores after OHE in cats receiving *s.c.* meloxicam alone or *s.c.* meloxicam and a buprenorphine transdermal patch. However, our results should be subject to careful interpretation as the study was limited by the small number of samples and by observer subjectivity.

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