FULL PAPER *Internal Medicine*

Influence of Preemptive Analgesia with Meloxicam before Resection of the Unilateral Mammary Gland on Postoperative Cardiovascular Parameters in Dogs

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ABSTRACT. Preemptive analgesia is recommended in small animal medicine. However, many studies have evaluated the response to analgesic treatment by behavioral observation. Therefore, the influence of preemptive analgesia with meloxicam on postoperative cardiovascular and renal parameters remains to be clarified. The present study examined the changes in blood pressure, heart rate, double product and heart rate variability for 14 days and the changes in glomerular filtration rate (GFR) and serum cortisol level for 24 hr after resection of the unilateral mammary gland in meloxicam and control groups consisting of 5 healthy dogs. All data were collected under unanesthetized and unrestrained conditions using a radio telemetry system. Blood pressure, heart rate and double product were significantly lower in the meloxicam compared with the control group, and the meloxicam group's diurnal changes became stable more than 36 hr earlier than those of the control group. The systolic, diastolic and mean blood pressure values of the meloxicam group were 5- to 20-mm Hg lower than those of the control group until 5 days after surgery. The maximum difference between the two groups in terms of the double product values 14 days after surgery was 2,000 bpm × mmHg. Autonomic activity inhibition was prolonged in the control group. There were no significant differences in the 24-hr changes in GFR or serum cortisol level. This study showed that perioperative administration of meloxicam reduced unfavorable postoperative changes in the cardiovascular system without influencing renal function.
KEY WORDS: canine, cardiovascular parameters, meloxicam, preemptive analgesia, telemetry system.

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Meloxicam is the first injectable COX-2 selective nonsteroidal anti-inflammatory drug extensively used in Japan. Many studies have reported the efficacy of preoperative meloxicam treatment in terms of surgical invasiveness [6, 8, 12, 14, 20]. In these studies, pain was mainly evaluated based on scoring systems, such as the visual analog scale (VAS) and cumulative pain score (CPS). However, these parameters were established based on subjective evaluation methods used in humans, and the results for these parameters differ among observers [12]. A study involving human infants reported no correlation between pain assessment by behavioral observation and subjective pain assessment [2].

Tumor resection is frequently performed in veterinary practice. Tumors are mostly found in older dogs, and one-third of elderly dogs have valvular disorders [5]. It is well known that pain is the cause of hypertension in human and animals [4]. In dogs, surgery-related pain may also increase blood pressure. However, only a limited number of studies have reported postoperative changes in the blood pressure of dogs [18], and no studies have indicated the influence of analgesic treatment on blood pressure changes.

Total resection of the unilateral mammary gland is the prevailing surgical procedure for aged female dogs in small animal medicine because mammary gland tumors are one of the most common tumors among female dogs [22]. The present study investigated the influence of surgical invasiveness during resection of the unilateral mammary gland and preemptive treatment with meloxicam on cardiovascular and renal parameters of dogs.

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MATERIALS AND METHODS

Animals: Five healthy female Beagles (mean age of 2.0 ± 0.7 years, mean weighing of 10.5 ± 1.8 kg) were used in this study. These dogs were confirmed to be healthy based on the results of physical examinations, complete blood counts and serum chemistry analyses. They were acclimated for 2 weeks under the experimental conditions at the Laboratory of Veterinary Internal Medicine, School of Veterinary Medicine, Nippon Veterinary and Life Science University.

Experimental environment: The dogs were housed in individual stainless steel cages measuring 710 (W) × 1,095 (D) × 795 (H) mm. The cages were kept under environmental conditions similar to those for household animals; entry to the room was unlimited (7:00–24:00), and room temperature nor lighting cycle were not controlled. Food (Hill's Science Diet Canine Maintenance) was given twice daily (9:30 and 17:00). Water was given *ad libitum*.

Telemeter implantation: A blood pressure (BP) telemetry system (Data Sciences International, st. paul, MN, U.S.A.) was used according to the report by Mishina *et al.* [18]. The dogs were premedicated with diazepam (0.5 mg/kg IV) and butorphanol (0.1 mg/kg IV) and given a lactated Ringer's solution infusion (5 to 10 mL/kg/hr) prior to induction of anesthesia with thiamylal sodium (25 mg/kg, IV). Anesthesia was maintained with isoflurane in 100% oxygen delivered through an endotracheal tube. A transmitter (TA11PA-

Table. 1. Telemeter implantation and the schedule for surgery in the control and experimental groups

Day	Event	Analgesia
Day -14	Telemeter implantation	Butorphanol and meloxicam
Day 0	Left side mammary gland resection	Butorphanol
Day 0–13	Experimantal period	
Day 14–20	Rest period	
Day 21	Right side mammary grand resection	Butorphanol and meloxicam
Day 21–34	Experimental period	

D70) was implanted into a subcutaneous pocket formed in the dog's right flank. The attached catheter was inserted approximately 15 cm into the caudal femoral artery. The dogs received standard postoperative care. The animals were allowed to recover for 2 weeks to avoid the effects of surgery to implant the telemeters.

Experimental design (Table 1): The dogs received butorphanol (0.1 mg/kg IV) just before surgery to extirpate the left mammary (control group). Systolic BP (SBP), mean BP (MBP), diastolic BP (DBP) and heart rate (HR) were then continuously recorded in the conscious, unrestrained dogs over the subsequent 2-week period as the changing phase [18, 19]. After a subsequent rest period of 1 week, the dogs received meloxicam (0.2 mg/kg SC) and butorphanol 2 hr before surgery to resect the right mammary gland (meloxicam group). The aforementioned parameters were then continuously recorded for the dogs over the subsequent 2-week period.

Resection of the mammary gland: Anesthesia was induced and maintained with the preceding procedure. Resection of the unilateral mammary gland was performed according to the standard method [11].

Measurement of BP, HR and autonomic activity: Data was received from the telemeter by a receiver (RMC-1), sent to a calibrated pressure analog adapter (R11CPA), and then sent to a PowerLab (ML820 PowerLab 2/20, ADInstruments, Inc., Colorado springs, CO, U.S.A.). The data was analyzed with the proprietary software (Chart 4.2.3, ADInstruments, Inc.). SBP, MBP, DBP and HR were continuously recorded. The collected data was averaged for 5-min periods. Double product (DP), the parameter of myocardial oxygen consumption, was calculated determining the SBP and HR. The high-frequency component (HF) and low-frequency/high-frequency ratio (LF/HF) of heart rate variability (HRV) were determined using analysis software (SRV-2W ver. 5.1, Softron, Tokyo, Japan) in order to evaluate the function of the autonomic nervous system [15, 21]. Frequencies ranging from 0.04 to 0.1 Hz were regarded as LF, and those ranging from 0.1 to 0.6 Hz were regarded as HF [15].

Measurement of the glomerular filtration rate: The glomerular filtration rate (GFR) was measured during the preoperative, intraoperative and postoperative periods and at 6, 12, and 24 hr after awakening using a 1-hr intrinsic creatinine clearance test.

Measurement of cortisol: In relation to resection of the mammary gland, the cortisol level was measured as a parameter of stress during the preoperative period, on extubation, and 1, 2, 4, 8, 12 and 24 hr after surgery. Serum was stored at –83°C until measurement. The cortisol level was measured using a Spotchem Vidas SV-5010 fluorescent immunoassay unit (Kyoto Daiichi Science Co., Ltd. Kyoto, Japan).

Statistical analysis: The values of BP, HR, DP, LF/HF and HF were expressed as 72-segment moving-averages for changes in the means obtained at 5-min intervals. The values for GFR and serum cortisol level were expressed as the mean ± standard deviation (SD). Data analysis was performed using computer software (JMP ver. 5.0.1, SAS Institute Inc., Cary, NC, U.S.A.). Serial changes in the data were compared using repeated measures one-way ANOVA. The means values of SBP, DBP, MBP, HR, DP, LF/HF and HF 24 hr after surgery were compared using the Student's *t*-test. We speculated that administration of an analgesic would decrease BP, HR and LF/HF and that it would increase HF. Therefore, the one-tailed Student's *t*-test was employed. $P<0.05$ was regarded as significant.

RESULTS

Changes in blood pressure: The serial changes in SBP, DBP and MBP of the control group were significantly higher than those of the meloxicam group ($P<0.0001$, respectively).

The mean values for BP 24 hr after surgery were also significantly higher in the control group (Table 2).

The SBP, DBP and MBP values of the meloxicam group decreased linearly by approximately 30 mm Hg between 12 and 36 hr after surgery; SBP dropped from approximately 190 mm Hg to 160 mm Hg, DBP dropped from approximately 120 mm Hg to 165 mm Hg, DBP dropped from approximately 130 mm Hg to 100 mm Hg and MBP dropped from approximately 150 mm Hg to 120 mm Hg. These values also decreased by approximately 30 mm Hg between 12 and 36 hours after surgery in the control group; SBP dropped from approximately 195 mm Hg to 165 mm Hg, DBP dropped from approximately 130 mm Hg to 100 mm Hg and MBP dropped from approximately 150 mm Hg to 120 mm Hg. However, the decreases were not linear, and there was a marked increase during the daytime. The above parameters began to gradually decrease in the two groups three days after surgery and exhibited diurnal changes (30

Table 2. Mean and P values of SBP, DBP, MBP, HR and DP of the dogs 24 hr after surgery

	SBP	DBP	MBP	HR	DP
Meloxicam	173.7 ± 26.3	109.2 ± 15.8	130.7 ± 19.2	125.3 ± 24.4	22097.8 ± 6507.3
Control	185.8 ± 22.2	118.3 ± 13.1	140.8 ± 15.9	123.4 ± 23.0	22984.7 ± 5462.0
P value	0.04240	0.07160	0.09520	0.74310	0.56840

Values are means ± SD.
SBP=systolic blood pressure. DBP=diastolic blood pressure. MBP=mean blood pressure. HR=heart rate. DP=double product.
Unit: SBP, DBP and MBP=mmHg. HR=bpm. DP=mmHg × bpm.

mm Hg).

Two days after surgery, the SBP, DBP and MBP of the control group were 10–20-mm Hg higher than those of the meloxicam group. These parameters were 5 to 10 mm Hg higher in the control group than in the meloxicam group from day 3 to day 5 after surgery. There were no marked differences between the two groups beginning six days after surgery. However, the values of SBP, DBP and MBP were higher again in the control group from day 7 (afternoon) until day 8 after surgery and from day 9 (afternoon) to day 10 (morning) after surgery.

The values reached a plateau in the meloxicam group during the afternoon 12 days after surgery. However, there was only a slight diurnal change in the control group 14 days after surgery; each parameter showed a slightly higher daily minimum (Figs. 1a-1c).

Changes in HR: The serial changes in the HR in the control group were significantly higher than those of the meloxicam group (P<0.0001). There was no significant difference in mean HR 24 hr after surgery (Table 2).

The 72-interval moving-averages of the control and meloxicam groups decreased linearly by approximately 60 and 90 bpm, respectively, over the course of 19 hr after surgery; the control group decreased from approximately 170 bpm to 100 bpm and the meloxicam group decreased from approximately 195 bpm to 105 bpm. Thereafter, the diurnal changes became stable 9 days after surgery in the meloxicam group and 12 days after surgery in the control group; there were marked differences from 9 (afternoon) to 12 days (morning) after surgery (Fig. 1d).

Changes in DP: The serial changes in DP in the control group were significantly higher than that in the meloxicam group (P<0.0001). There was no significant difference in the mean value 24 hr after surgery (Table 2).

The 72-segment moving averages of the 2 groups decreased linearly from approximately 30,000 to 16,000 bpm x mm Hg over the course of 19 hr after surgery. The meloxicam and control groups exhibited bimodal diurnal changes from 3 and 2 days after surgery, respectively. Thereafter, the values gradually decreased and became stable in the afternoon 9 and 12 days after surgery in the meloxicam and control groups, respectively.

The 72-segment moving-averages of the control group at all time points 2 days or more after surgery were higher than those in the meloxicam group, with a maximum difference of 2,000 bpm × mm Hg 14 days after surgery (Fig. 1e).

LF/HF ratio: The serial changes in the LF/HF ratio of the meloxicam group were significantly higher than those of the control group (P=0.0025). In particular, the peaks immediately after surgery were 0.5800 ± 0.7609 and 0.9621 ± 1.0623 msec^2 in the control and meloxicam groups, respectively. Thereafter, the values of the 2 groups decreased linearly until 3 hr after surgery, exhibited diurnal changes and increased step by step. The 2 groups exhibited stable diurnal changes biginning 11 days after surgery (Fig. 1f).

Changes in the HF: There were no significant differences between the serial changes in HF of the meloxicam and control groups (P=1.0000). The HF values of the two groups increased linearly to peaks of 10,662.60 ± 5,594.40 msec^2 (7:28:56) and 23,690.60 ± 23,175.20 msec^2 (7:48:40) 19 hr after surgery, respectively. Thereafter, the 2 groups exhibited diurnal changes involving a peak at 4:00 a.m. to 7:00 a.m. There were marked diurnal changes in the meloxicam group until 6 days after surgery. However, the peak gradually increased beginning 7 days after surgery. There was no stable increase in the control group within 4 days after surgery (Fig. 1g).

Changes in the serum cortisol level: There were no significant differences between the serial changes in cortisol level of the meloxicam and control groups (p=0.2358). The preoperative cortisol levels were 9.14 ± 12.1 μg/dL (meloxicam) and 12.9 ± 15.6 μg/dL (control), and they increased to 28.1 ± 30.6 μg/dL and 30.1 ± 33.4 μg/dL on extubation, respectively. The value for the meloxicam group gradually decreased thereafter and ranged from 7.63 ± 8.2 to 10.9 ± 14.6 μg/dL beginning 4 hr after surgery. In the control group, the value ranged from 13.4 ± 14.3 to 18.8 ± 25.2 μg/dL between 4 and 12 hr after surgery, and then increased to 27.5 ± 57.0 μg/dL 24 hr after surgery (Fig. 4).

Changes in GFR: There were no significant differences between the serial changes in GFR of the meloxicam and control groups (P=0.0631). The preoperative GFR value of the meloxicam group was 2.54 ± 0.64 mL/kg/min. It decreased to 1.55 ± 0.72 mL/kg/min during surgery, but then increased to the preoperative value 24 hr after surgery. Similar changes were also observed in the control group. However, the values were higher than those in the meloxicam group; the preoperative GFR value was 3.12 ± 2.94 mL/kg/min. It decreased to 2.25 ± 1.30 mL/kg/min during surgery, but then increased to the preoperative value 24 hr after surgery (Fig. 5).

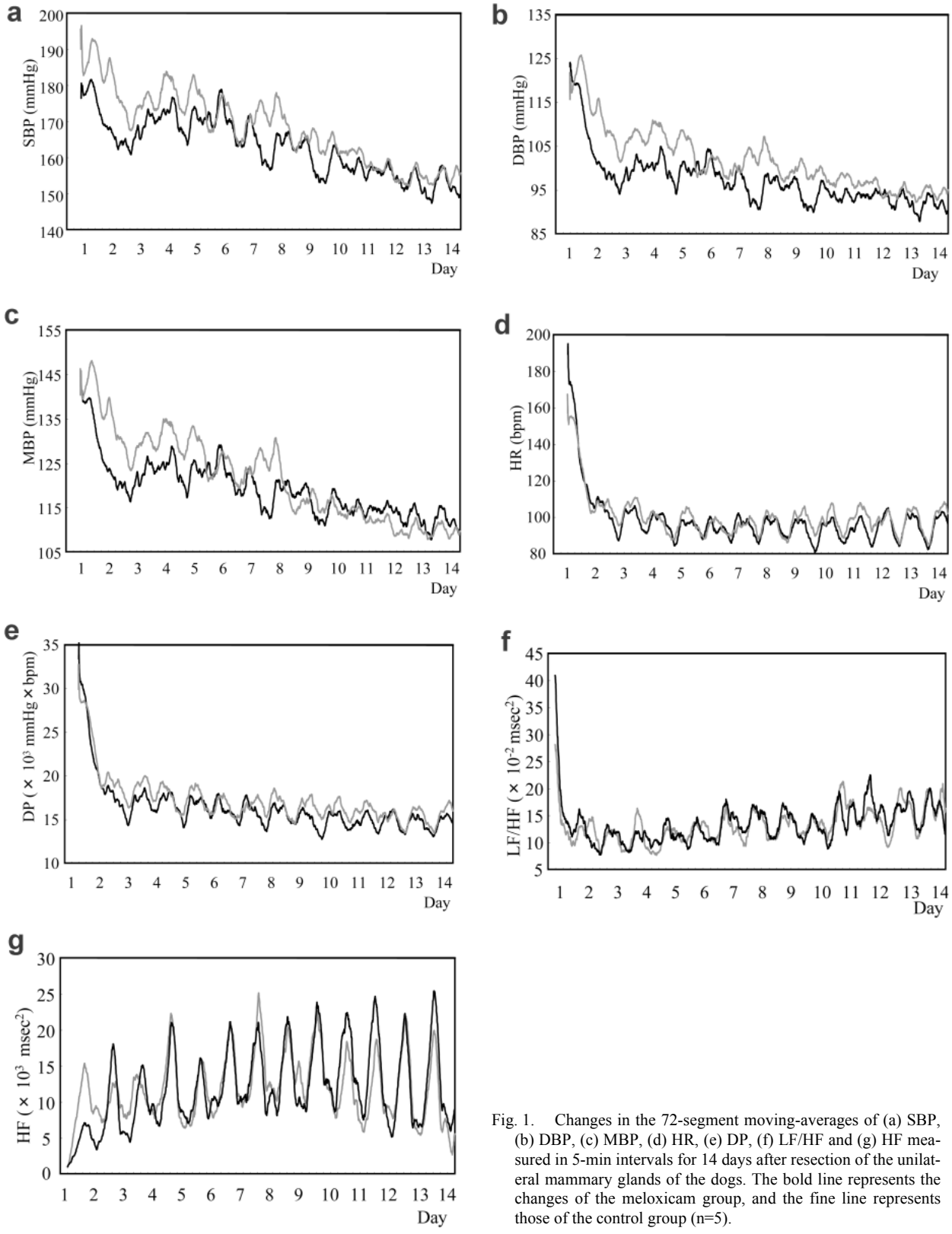

Fig. 1. Changes in the 72-segment moving-averages of (a) SBP, (b) DBP, (c) MBP, (d) HR, (e) DP, (f) LF/HF and (g) HF measured in 5-min intervals for 14 days after resection of the unilateral mammary glands of the dogs. The bold line represents the changes of the meloxicam group, and the fine line represents those of the control group (n=5).

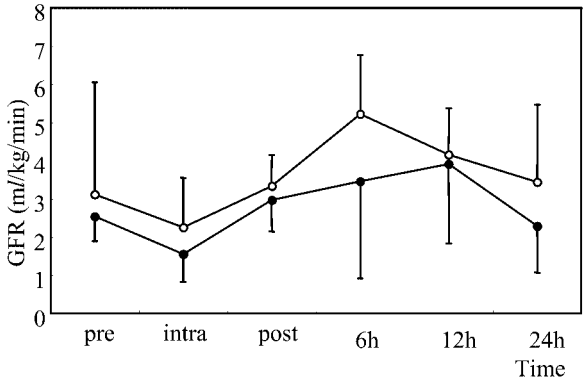

Fig. 2. Changes in the serum cortisol levels of the dogs during the preoperative period for the unilateral mammary gland (pre), on extubation (ex), and 1, 2, 4, 8, 12 and 24 hr after surgery. The closed circles represent the changes of the meloxicam group, and the open circles represent those of the control group (mean ± SD; n=5).

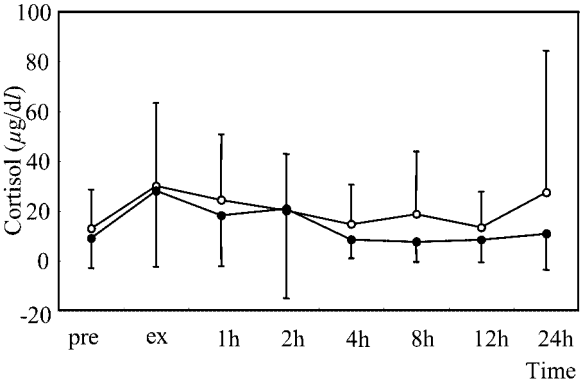

Fig. 3. Changes in GFR during the preoperative period for the unilateral mammary gland (pre), intraoperative period (intra), postoperative period (post) and 6, 12 and 24 hr after surgery. The closed circles represent the changes of the meloxicam group, and the open circles represent those of the control group (mean ± SD; n=5).

DISCUSSION

To our knowledge, this is the first study to investigate the serial changes in postoperative BP, HR, LF/HF and HF in dogs.

In this experiment, the SBP, DBP, MBP, HR and DP values of the meloxicam group were significantly lower than those of the control group. The BP of the meloxicam group decreased until 36 hr after surgery and then stabilized beginning 12 days after surgery. In the control group, the diurnal changes in BP immediately after surgery deviated from the physiological range and remained unstable beginning 12 days after surgery. The HR and DP of the meloxicam group returned to the within the physiological ranges 36 hr earlier. These results suggest that the cardiovascular system is loaded for a long period in the absence of meloxicam. Hypertension is one of the risk factors for cardiovascular disorders [13]. Therefore, meloxicam should be administered before surgery to prevent hypertension-related heart disease even in normotensive animals without heart disease because the age of dogs at tumor detection is advanced and valvular disorders frequently develop in elderly dogs [5]. In this study, a single dose of meloxicam was administered before surgery, and its half-life was 24 hr [7]. This may have been associated with the difference in the BP changes between the 2 groups 36 hr after surgery. Thereafter, BP was high and stable for 4 days; therefore, repeated postoperative administration of meloxicam may decrease BP to within the physiological range in a shorter period.

Acute pain stimuli through a somatosensory reflex increases sympathetic arousal and produces increased BP [4]. Elevated BP might be associated with enhanced activation of the pain inhibitory pathway in the context of brief pain [4], but might also be associated with greater activation of the pain facilitory pathway in response to more prolonged pain [4]. Preemptive analgesia with meloxicam inhibits synthesis of prostaglandin E_2 and I_2, and might prevent prolonged pain and consequently hypertension. An imbalance between sympathetic and parasympathetic activities may also have been associated with hypertension after surgery. The LF/HF reduction of the meloxicam group was relieved, and HF became stable 12 days after surgery. The LF/HF ratio of the control group stabilized 12 days after surgery, but the HF remained unstable.

Surgical invasiveness influenced the changes in the BPs of the meloxicam and control groups until 12 days after surgery. This finding suggests that the influence of surgical invasiveness persists even in grossly normal dogs after surgery. Subjective evaluation methods such as VAS should be applied carefully.

Böstrom *et al.* [3] reported that there is no difference in GFR between Beagles treated with meloxicam before anesthesia and control Beagles. In the present study, although the GFR of both groups declined, there was no significant difference between the groups.

There were also no significant differences in serum cortisol level between the 2 groups. However, the cortisol level in the meloxicam group was lower from 4 to 24 hr after surgery.

One limitation of this experiment was that it only included young dogs due to the difficulty in using aged experimental dogs. To our knowledge, the effect of age on canine BP has not been explored [1, 9, 10, 16, 17, 23, 24]. In the future, an additional experiment should be conducted that includes elderly dogs, which have a higher incidence of cardiovascular disease and neoplasm.

In our experiment, perioperative treatment with meloxicam relieved postoperative changes in cardiovascular parameters without affecting the kidney, which suggests the necessity of this treatment.

REFERENCES

1. Bodey, A. R. and Michell, A. R. 1996. Epidemiological study

of blood pressure in domestic dogs. *J. Small Anim. Pract.* **37**: 116–125.
2. Beyer, J. E., McGrath, P. J. and Berde, C. B. 1990. Discordance between self-report and behavioral pain measures in children aged 3–7 years after surgery. *J. Pain Symptom Manage.* **5**: 350–356.
3. Böstrom, I. M., Nyman, G., Hoppe, A. and Lord, P. 2006. Effects of meloxicam on renal function in dogs with hypotension during anaesthesia. *Vet. Anaesth. Analg.* **33**: 62–69.
4. Bruehl, S. and Chung, O. Y. 2004. Interactions between the cardiovascular and pain regulatory systems: an updated review of mechanisms and possible alterations in chronic pain. *Neurosci. Biobehav. Rev.* **28**: 395–414.
5. Buchanan, J. W. 1999. Prevalence of cardiovascular disorders. pp. 457–470. *In*: Text Book of Canine and Feline Cardiology, 2nd ed. (Fox, P. R., Sisson, D. and Moise, N. S. eds.), W.B. Saunders Company, Pennsylvania.
6. Budsberg, S. C., Cross, A. R., Quandt, J. E., Pablo, L.S. and Runk, A. R. 2002. Evaluation of intravenous administration of meloxicam for perioperative pain management following stifle joint surgery in dogs. *Am. J. Vet. Res.* **63**: 1557–1563.
7. Busch, U., Schmid, J., Heinzel, G., Schmaus, H., Baierl, J., Huber, C. and Roth, W. 1998. Pharmacokinetics of meloxicam in animals and the relevance to humans. *Drug. Metab. Dispos.* **26**: 576–584.
8. Deneuche, A. J., Dufayet, C., Goby, L., Fayolle, P. and Desbois, C. 2004. Analgesic comparison of meloxicam or ketoprofen for orthopedic surgery in dogs. *Vet. Surg.* **33**: 650–660.
9. Haidet, G. C., Wennberg, P. W. and Rector, T. S. 1995. Aging and vasoreactivity: *in vivo* responses in the beagle hindlimb. *Am. J. Physiol.* **268**: H92–H99.
10. Haidet, G. C., Wennberg, P. W., Finkelstein, S. M. and Morgan, D. J. 1996. Effects of aging per se on arterial stiffness: systemic and regional compliance in beagles. *Am. Heart. J.* **132**(2 Pt 1): 319–327.
11. Hedlund, C. S. 2002. Surgery of the reproductive and genital systems. pp. 610–674. *In*: Small Animal Surgery (Fossum, T. W. ed.), Mosby, Missouri
12. Leece, E. A., Brearley, J. C. and Harding, E. F. 2005. Comparison of carprofen and meloxicam for 72 hr following ovariohysterectomy in dogs. *Vet. Anaesth. Analg.* **32**: 184–192.
13. Littman, M. P. 1999. Systemic hypertension: recognition and treatment. pp. 795–813. *In*: Text Book of Canine and Feline Cardiology, 2nd ed. (Fox, P. R., Sisson, D. and Moise, N. S. eds.), W.B. Saunders Company, Pennsylvania.
14. Mathews, K. A., Pettifer, G., Foster, R. and McDonell, W. 2001. Safety and efficacy of preoperative administration of meloxicam, compared with that of ketoprofen and butorphanol in dogs undergoing abdominal surgery. *Am. J. Vet. Res.* **62**: 882–888.
15. Matsunaga, T., Harada, T., Mitsui, T., Inokuma, M., Hashimoto, M., Miyauchi, M., Murano, H. and Shibutani, Y. 2001. Spectral analysis of circadian rhythms in heart rate variability of dogs. *Am. J. Vet. Res.* **62**: 37–42.
16. Meurs, K. M., Miller, M. W., Slater, M. R. and Glaze, K. 2000. Arterial blood pressure measurement in a population of healthy aged dogs. *J. Am. Anim. Hosp. Assoc.* **36**: 497–500.
17. Mishina, M., Watanabe, T., Fujii, K., Maeda, H., Wakao, Y. and Takahashi, M. 1997. A clinical evaluation of blood pressure through non-invasive measurement using the oscillometric procedure in conscious dogs. *J. Vet. Med. Sci.* **59**: 989–993.
18. Mishina, M., Watanabe, T., Matsuoka, S., Shibata, K., Fujii, K., Maeda, H. and Wakao, Y. 1999. Diurnal variations of blood pressure in dogs. *J. Vet. Med. Sci.* **61**: 643–647.
19. Miyazaki, H., Yoshida, M., Samura, K., Matsumoto, H., Ikemoto, F. and Tagawa, M. 2002. Ranges of diurnal variation and the pattern of body temperature, blood pressure and heart rate in laboratory beagle dogs. *Exp. Anim.(Tokyo)* **51**: 95–98.
20. Moreau, M., Dupuis, J., Bonneau, N. H. and Desnoyers, M. 2003. Clinical evaluation of a nutraceutical, carprofen and meloxicam for the treatment of dogs with osteoarthritis. *Vet. Rec.* **152**: 323–329.
21. Rimoldi, O., Pierini, S., Ferrari, A., Cerutti, S., Pagani, M. and Malliani, A. 1990. Analysis of short-term oscillations of R-R and arterial pressure in conscious dogs. *Am. J. Physiol.* **258**: H967–H976.
22. Rutteman, G. R., Withrow, S. J. and MacEwen, E. G. 2001. Tumors of the mammary gland. pp. 455–477. *In*: Small Animal Clinical Oncology, 3rd ed. (Withrow, S. J. and MacEwan, E. G. eds.), Saunders, Pennsylvania.
23. Smolensky, M. H. and Portaluppi, F. 1996. Ambulatory Blood Pressure Monitoring. Application to Clinical Medicine and Antihypertension Medication Trials. *Ann. New York Acad. Sci.* **783**: 279–294.
24. Yin, F. C. P., Weisfeldt, M. L. and Milnor, W. R. 1981. Role of aortic input impedance in the decreased cardiovascular response to exercise with aging in dogs. *J. Clin. Invest.* **68**: 28–38.