Cardiorespiratory responses and plasma cortisol concentrations in dogs treated with medetomidine before undergoing ovariohysterectomy

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Objective—To evaluate effects of medetomidine on anesthetic dose requirements, cardiorespiratory variables, plasma cortisol concentrations, and behavioral pain scores in dogs undergoing ovariohysterectomy.

Design—Randomized, prospective study.

Animals—12 healthy Walker-type hound dogs.

Procedure—Dogs received medetomidine (40 µg/kg [18.2 µg/lb] of body weight, IM; n = 6) or saline (0.9% NaCl) solution (1 ml, IM; 6) prior to anesthesia induction with thiopental; thiopental dose needed for endotracheal intubation was compared between groups. Ovariohysterectomy was performed during halothane anesthesia. Blood samples were obtained at various times before drug administration until 300 minutes after extubation. Various physiologic measurements and end-tidal halothane concentrations were recorded.

Results—In medetomidine-treated dogs, heart rate was significantly lower than in controls, and blood pressure did not change significantly from baseline. Plasma cortisol concentrations did not increase significantly until 60 minutes after extubation in medetomidine-treated dogs, whereas values in control dogs were increased from time of surgery until the end of the recording period. Control dogs had higher pain scores than treated dogs from extubation until the end of the recording period.

Conclusion and Clinical Relevance—Administration of medetomidine reduced dose requirements for thiopental and halothane and provided postoperative analgesia up to 90 minutes after extubation. Dogs undergoing ovariohysterectomy by use of thiopental induction and halothane anesthesia benefit from analgesia induced by medetomidine administered prior to anesthesia induction. Additional analgesia is appropriate 60 minutes after extubation. (*J Am Vet Med Assoc* 2000;217:509–514)

Medetomidine is an α_2-adrenergic agonist with sedative, analgesic, and muscle relaxant properties.[1-4] It has been used alone or in combination with other anesthetic agents such as ketamine or opioids in dogs.[2-4] Medetomidine administered before general anesthesia reduces dosage requirements of anesthetic induction and maintenance agents.[5-8] Furthermore, it has been observed that postoperative administration of medetomidine has better analgesic effect than buprenorphine in alleviating pain caused by thoracotomy in dogs.[9] Recent evidence supports the concept of preemptive analgesia by administration of analgesic agents prior to the initiation of a nociceptive stimulus, therefore, inhibiting the perception of pain.[10-12] However, the use of medetomidine as a preemptive analgesic agent has not been reported.

Plasma cortisol concentration is a commonly used measurement of pain-induced distress in dogs after **ovariohysterectomy (OHE)**.[13-14] It is not known whether administration of medetomidine prior to OHE will reduce plasma cortisol concentrations after surgery under halothane anesthesia. Furthermore, a direct comparison of cardiorespiratory effects in dogs with or without medetomidine administration followed by halothane anesthesia for OHE has not been explored. The purpose of the study reported here was to evaluate the effects of medetomidine premedication on anesthetic dose requirements, cardiorespiratory variables, plasma cortisol concentrations, and behavioral pain scores in dogs undergoing OHE.

Materials and Methods

Twelve 2.5-year-old healthy Walker-type hound dogs weighing 17 to 22.5 kg were equally allocated to treatment with medetomidine[a] (40 µg/kg [18.2 µg/lb] of body weight, IM) or saline (0.9% NaCl) solution (1 ml, IM) administered 20 minutes prior to induction of anesthesia with thiopental.[b] The calculated dose of thiopental was 3 or 15 mg/kg (1.36 or 6.8 mg/lb; IV) for medetomidine- or saline solution-treated groups, respectively. The actual induction dose needed for endotracheal intubation for each dog was recorded and compared between the 2 groups. Following endotracheal intubation, anesthesia was maintained by administration of halothane in 100% oxygen. The same experienced surgeon performed OHE on all dogs. Total duration of anesthesia and surgery was recorded for each dog and compared between the 2 treatment groups. Prior to each trial, a 4.45-cm, 20-gauge catheter[c] was placed in the cephalic vein for drug administration and collection of blood samples for measurement of plasma cortisol concentrations. A lead-II ECG[d] was monitored before induction and continuously throughout the experiment until the dog was moved to the recovery area. Blood pressure was measured noninvasively by use of an oscillometric technique,[e] with the cuff placed around the antebrachium. **Heart rate (HR)**, **systolic**, **diastolic**, and **mean blood pressures (SBP, DBP, MBP,** respectively), **respiratory rate (RR)**, and rectal temperature were recorded before drug administration as well as immediately after thiopental induction, skin incision, removal of the second

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ovary, extubation, and 30, 60, 90, 120, 150, 180, and 300 minutes after extubation. A pulse oximeter[f] was used to monitor arterial hemoglobin oxygen saturation during surgery, with the monitoring probe placed on the dog's tongue. End-tidal halothane concentrations were also monitored via an anesthetic agent monitor[d] during anesthesia. Dogs were moved to a recovery area after surgery. Body temperature was maintained by use of a towel and heating blanket during the surgery and recovery periods. Coughing and gagging stimulated by the endotracheal tube was used as an end point for extubation. Following extubation, 2 observers who were blinded to the treatments evaluated dogs' behavioral responses to postsurgical pain (**Appendix**). Mean values for pain scores from both observers for each recording time were determined.

Blood samples for plasma cortisol assessment were obtained at the same time intervals and prior to recording of cardiorespiratory measurements. Blood samples were centrifuged, and plasma was removed and stored at –20 C until assayed 1 week later. Total plasma cortisol concentrations were determined by radioimmunoassay[g] in a commercial laboratory.[h] Briefly, 25 µl of plasma was pipetted into antibody-coated tubes, and 1 ml of cortisol labeled with I 125 was added to all tubes. Tubes were vortexed and incubated for 45 minutes in a water bath at 37 C. Samples were decanted and counted for 1 minute in a gamma counter. The lowest detectable concentration was 0.2 ng/ml, and intra-assay and interassay coefficients of variation were 4.4 and 5.6%, respectively.

Statistical analyses—A repeated measures mixed general linear mode was used to analyze cortisol concentration, SBP, DBP, MBP, HR, RR, and rectal temperature with random effects of animal and period. Trapezoidal method was used to calculate area under the curve of the plasma cortisol values over time (integrated cortisol value). Pairwise comparisons between treatments were made for each data collection time point. Behavioral pain scores were analyzed by use of the Cochran-Mantel-Haenszel test at each time point. Row Mean Scores Differ statistic was used to detect significant ($P < 0.05$) difference between treatment groups.

Results

Anesthesia effects—Induction dose for thiopental was significantly lower in the medetomidine group than in the control group (**Table 1**). Medetomidine-treated dogs appeared deeply sedated, which made preparation and positioning for catheterization and anesthetic induction easy, compared with control dogs. End-tidal halothane concentration was also significantly lower in the medetomidine group than the control group during surgery. Duration of inhalational anesthesia (from anesthesia induction to completion of surgery) was not significantly different between the 2 treatment groups. All dogs maintained arterial hemoglobin oxygen saturation between 94 and 100% during halothane anesthesia. Time from termination of halothane anesthesia to time of extubation was significantly longer in the medetomidine group than the control group.

Table 1—Comparison of effects of preoperative administration of medetomidine (40 µg/kg [18.2 µg/lb] of body weight, IM) or saline (0.9% NaCl) solution (control; 1 ml, IM) on anesthetic and surgical variables during ovariohysterectomy in dogs

Anesthetic and surgical variables	Medetomidine	Control
Thiopental induction dose (mg/kg*)	4.4 ± 3.0†	14.8 ± 3.4
End-tidal halothane concentration (%)		
Induction	0.96 ± 0.28†	3.00 ± 0.28
Skin incision	0.88 ± 0.28†	3.08 ± 0.28
Ovary removal	1.42 ± 0.28†	3.71 ± 0.28
Extubation	0.03 ± 0.31	0.10 ± 0.31
Duration of anesthesia (min)	51.0 ± 5.5	48.0 ± 8.0
Time to extubation (min)‡	35.8 ± 16.4†	17.0 ± 8.8

*To convert to mg/lb, divide by 2.2. †Within a row, different superscripts indicate significant ($P < 0.05$) difference between groups. ‡Time from cessation of administration of halothane to extubation.
Data are expressed as mean ± SD values (n = 6 for each group).

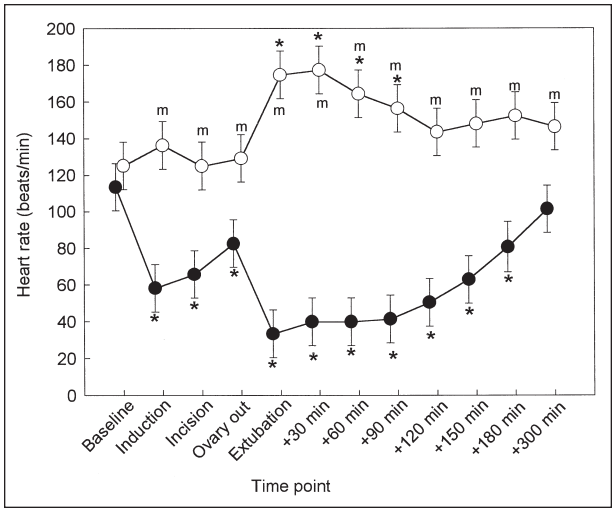

Figure 1—Heart rate (mean ± SD) in dogs treated with medetomidine (n = 6; solid circles) or physiologic saline (0.9% NaCl) solution (6; open circles) before anesthesia induced by administration of thiopental and halothane for ovariohysterectomy. *Value significantly ($P < 0.05$) different from baseline within group. m = Values significantly different between treatment groups. Values were determined at various time points from baseline to 300 minutes after extubation.

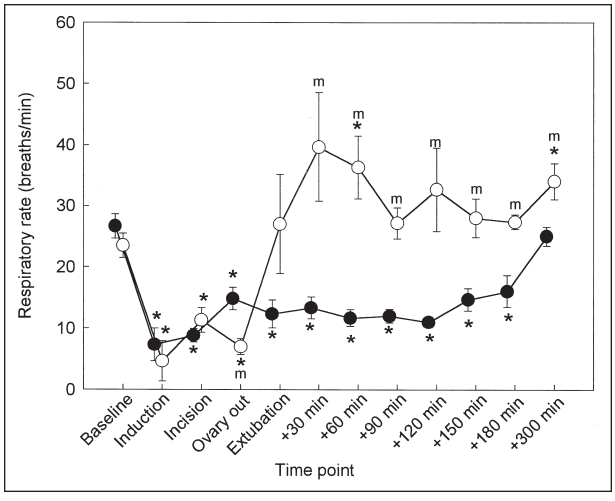

Figure 2—Respiratory rate (mean ± SD) in dogs treated with medetomidine (n = 6; solid circles) or physiologic saline solution (6; open circles) before anesthesia induced by administration of thiopental and halothane for ovariohysterectomy. *See* Figure 1 for key.

Cardiovascular measurements—Baseline HR was not significantly different between the 2 treatment groups (**Fig 1**). Heart rate decreased significantly after medetomidine administration and did not return to

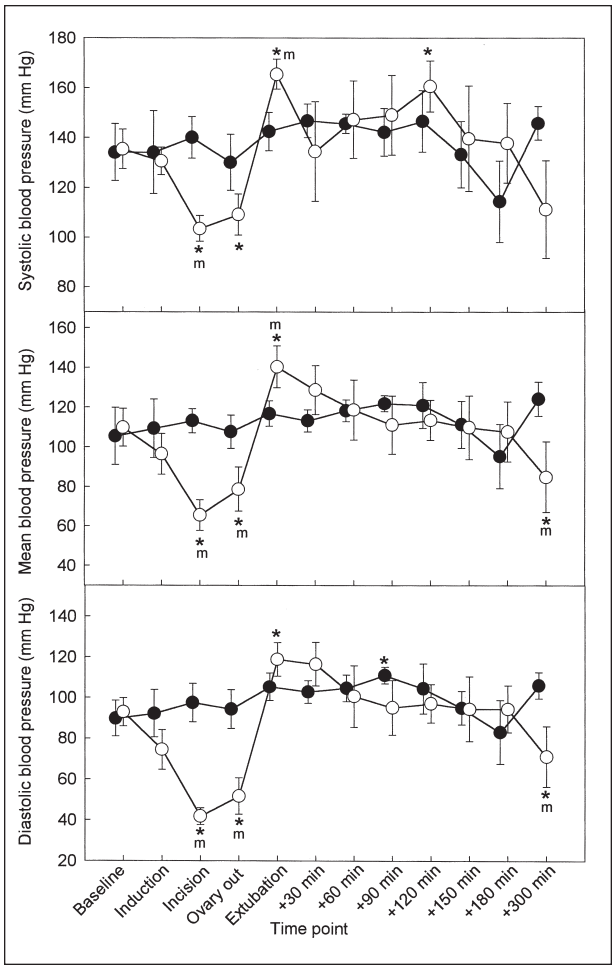

Figure 3—Blood pressure (mean ± SD) in dogs treated with medetomidine (n = 6; solid circles) or physiologic saline solution (6; open circles) before anesthesia induced by administration of thiopental and halothane for ovariohysterectomy. *See* Figure 1 for key.

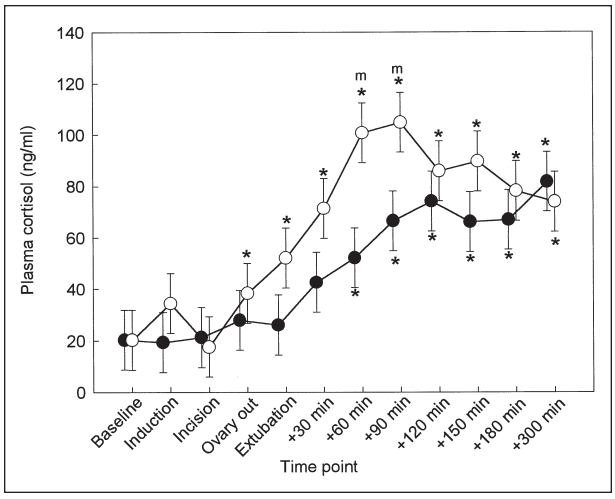

Figure 4—Plasma cortisol concentration (mean ± SD) in dogs treated with medetomidine (n = 6; solid circles) or physiologic saline solution (6; open circles) before anesthesia induced by administration of thiopental and halothane for ovariohysterectomy. *See* Figure 1 for key.

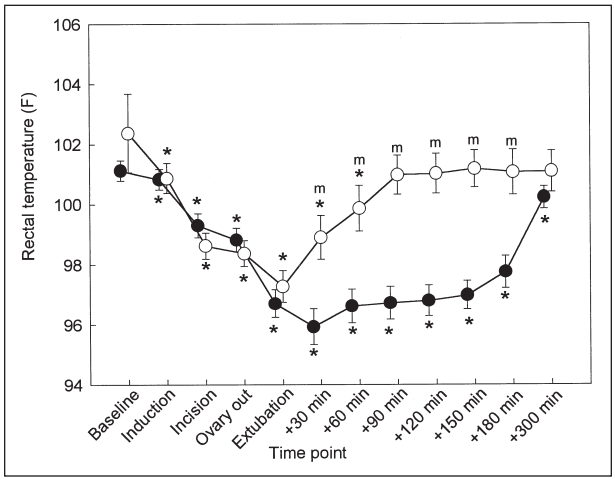

Figure 5—Rectal temperature (mean ± SD) in dogs treated with medetomidine (n = 6; solid circles) or physiologic saline solution (6; open circles) before anesthesia induced by administration of thiopental and halothane for ovariohysterectomy. To convert temperature to centigrade, subtract 32 and multiply by 5/9. *See* Figure 1 for key.

baseline values until 300 minutes after extubation in the medetomidine group. In contrast, HR increased significantly from baseline values in the control group from extubation to 120 minutes after extubation, and these values were significantly higher than those of the medetomidine group. Mean HR was higher during the intraoperative period than during the recovery period in the medetomidine group. In contrast, mean HR was lower during the intraoperative period than during the recovery period in the control group. For the medetomidine group, HR ranged from 31 to 103 beats/min during the intraoperative period and from 19 to 133 beats/min during the recovery period. For the control group, HR ranged from 84 to 222 beats/min during the intraoperative period and from 61 to 228 beats/min during the recovery period.

Respiratory rate was significantly higher in the control group than the medetomidine group 30 minutes after extubation and remained higher thereafter. Medetomidine-treated dogs had significant lower RR than the baseline values throughout the experiment (**Fig 2**).

Blood pressure remained stable and did not change significantly from baseline throughout the experimental period in the medetomidine group (**Fig 3**). Blood pressure fluctuated throughout the experimental period in the control group. Mean blood pressure decreased significantly from baseline values during the intraoperative period and then increased significantly from baseline at extubation in the control group. The MBP was significantly higher in the medetomidine group than in the control group during the intraoperative period.

Plasma cortisol concentration—Plasma cortisol concentration increased significantly from baseline value in the control group at the time of ovary manipulation and remained significantly increased to the end of the experiment (300 minutes after extubation). In contrast, plasma cortisol concentration did not change significantly from baseline value in the medetomidine group until 60 minutes after extubation (**Fig 4**).

Table 2—Behavioral pain scores during recovery from anesthesia (thiopental induction followed by halothane in oxygen) in dogs treated before ovariohysterectomy with medetomidine (M) or saline (S) solution

		Pain score*				
Time (min)	Treatment	1 (minimal pain)	2 (faint pain)	3 (mild pain)	4 (moderate pain)	5 (severe pain)
Extubation	S	—	—	5/6	—	1/6
	M	5/6	1/6	—	—	—
30	S	—	—	—	2/6	4/6
	M	5/6	—	—	1/6	—
60	S	—	—	—	2/6	4/6
	M	5/6	—	—	1/6	—
90	S	—	—	—	2/6	4/6
	M	4/6	1/6	—	1/6	—
120	S	—	—	—	2/6	4/6
	M	3/6	2/6	—	—	1/6
150	S	—	—	—	3/6	3/6
	M	2/6	3/6	—	—	1/6
180	S	—	—	—	3/6	3/6
	M	2/6	2/6	—	1/6	1/6
300	S	—	—	1/6	2/6	3/6
	M	1/6	3/6	—	1/6	1/6

*Values indicate proportion of dogs with signs of pain.
— = 0/6.

Furthermore, cortisol concentration was significantly lower in the medetomidine group than in the control group 60 and 90 minutes after extubation. The integrated cortisol value (area under the cortisol curve) was significantly lower in the medetomidine group (48,642 ± 14,071 ng/ml·h), compared with the control group (74,206 ± 9,543 ng/ml·h).

Rectal temperature and recovery characteristics—Rectal temperature significantly decreased from baseline values in both treatment groups (**Fig 5**). Medetomidine-treated dogs had significantly lower rectal temperature than control dogs from 30 to 180 minutes after extubation. The lowest recorded rectal temperature in the medetomidine group was 35.5 ± 0.3 C (95.9 ± 0.6 F) at 30 minutes after extubation. The lowest rectal temperature in the control group was 36.2 ± 0.2 C (97.3 ± 0.5 F) at extubation. Thereafter, rectal temperature returned toward baseline in both groups. Control dogs had significantly greater postoperative pain scores, compared with medetomidine-treated dogs at each time point (**Table 2**).

Discussion

Currently, available analgesic agents can be generally classified into 4 groups: local anesthetics, opioids, nonsteroidal anti-inflammatory drugs, and α_2-adrenergic agonists.[11,15] Medetomidine is an α_2-adrenergic agonist and is a suitable analgesic for treating mild to moderate acute pain.[9] Results of a recent study indicate that medetomidine induces better analgesia than buprenorphine in treating pain after thoracotomy in dogs.[9] Furthermore, medetomidine may also be used as a preemptive analgesic agent when administered prior to surgery. In addition to its analgesic benefit, medetomidine also induces a dose-dependent sedative effect.[1-4] In the study reported here, dogs treated with medetomidine had profound sedation that greatly facilitated handling, positioning, and preparation for anesthesia induction.

Medetomidine treatment also reduced the dose of thiopental and halothane required for endotracheal intubation and OHE; induction dose of thiopental in the medetomidine group was 4.4 ± 3.0 mg/kg (2 ± 1.4 mg/lb), compared with 14.8 ± 3.4 mg/kg (6.7 ± 1.5 mg/lb) in the control group. Mean thiopental induction dose required for endotracheal intubation following IM administration of 30 µg/kg (13.6 mg/lb) of medetomidine is 4.5 mg/kg (2 mg/lb) and 2.4 mg/kg (1.1 mg/lb) after administration of 40 µg/kg (18.1 µg/lb) of medetomidine.[16,17] Thiopental induction dose in the medetomidine group was slightly higher than that of a previous study but was significantly lower than the dose used in our control group. The concentration of halothane required for surgery was significantly lower in the medetomidine group than in the control group. This sparing effect is similar to that reported in previous studies in that medetomidine treatment reduces the minimal alveolar concentrations of halothane and isoflurane by > 90 and 47.2%, respectively, in dogs.[7,17-19] This sparing effect is by central α_2 receptors, because the effect is attenuated by the use of central-acting α_2 antagonists such as atipamezole.[7,17-19]

There was no significant difference in anesthesia duration (time from induction to completion of surgery and termination of halothane anesthesia) between the 2 groups. This finding suggests consistent intergroup surgical preparation and duration. Time from termination of halothane anesthesia to time of extubation was significantly longer in the medetomidine group, compared with the control group (35.8 ± 16.4 vs 17.0 ± 8.8 minutes, respectively), suggesting that there was a residual blood concentration of medetomidine that caused slower recovery from anesthesia. Dogs in the medetomidine group appeared mildly sedated after extubation. Rectal temperature decreased significantly from baseline values in both treatment groups; 35.5 ± 0.3 C (95.9 ± 0.6 F) was the lowest recorded value in the medetomidine group. Decreased rectal temperature may have resulted from a combination of anesthetic-induced depression of the thermoregulation center and heat loss from open

abdominal surgery. Attention should be given to maintenance of body temperature with this anesthetic protocol, because a heating blanket alone did not prevent hypothermia in the study reported here.

Heart rate decreased significantly after administration of medetomidine and was significantly lower than that of control dogs; HR did not return to baseline value until 300 minutes after extubation. It appears that concurrent administration of thiopental and halothane did not affect the bradycardia induced by medetomidine. Heart rate increased significantly from the baseline value in the control group from extubation to 90 minutes after extubation. A partial explanation may be that when the sympathetic attenuation or myocardial depressive effect from halothane was removed during the recovery period, sympathetic stimulation from postsurgical pain resulted in significant increase in HR for control dogs.

In the control group, MBP decreased significantly from the baseline value during the intraoperative period and increased significantly at extubation. These changes were not seen in the medetomidine group. Minimal changes in MBP in the medetomidine group during the intraoperative period may be attributable to the sparing effects of medetomidine, which reduce the required dose for thiopental and halothane, resulting in more stable blood pressure. The control group had significantly higher RR between 30 and 300 minutes after extubation, compared with the medetomidine group. This was most likely attributable to acute awareness of pain in the control group.

Pain-induced distress, as assessed by changes in plasma cortisol concentrations after OHE, persists for at least 5 hours after surgery in dogs when effective analgesia is not administered.[14] The cortisol concentrations, behavioral pain scores, and cardiorespiratory results of our study support this finding. Plasma cortisol concentration significantly increased from the baseline value in the control group at the time of ovary removal and remained increased to the end of the experiment. These results strongly suggest that dogs undergoing OHE with thiopental induction and halothane anesthesia will benefit from the administration of an additional analgesic agent either before or immediately after extubation.

Treatment with medetomidine before surgery attenuated the distress response up to 60 minutes after extubation in the dogs of the study reported here, as evidenced by plasma cortisol concentrations that did not change. Behavioral signs of pain were minimal at this time. Furthermore, the cortisol concentration was significantly lower in the medetomidine group than in the control group at 60 and 90 minutes after extubation. The arithmetic mean integrated cortisol value (area under the cortisol curve) was significantly lower in the medetomidine group, compared with the control group. On the basis of these findings, the authors suggest that a supplemental analgesic should be administered 60 minutes after extubation with this anesthetic protocol.

The Walker-type hound dogs used in the study reported here might be less sensitive to pain than other dogs (eg, miniature breeds) because of their stoic nature. In less stoic dogs, administration of a supplemental analgesic may need to be performed earlier than 60 minutes after extubation. It has been recommended that when a procedure is likely to cause postoperative pain, an analgesic agent should be administered regardless of an animal's behavior.[20] This is particularly true when risk from the use of analgesics is low, and there is uncertainty regarding the degree of postoperative pain the animal is experiencing.[20]

[a]Domitor, Pfizer Animal Health, Exton, Pa.
[b]Pentothal, Abbott Laboratories, North Chicago, Ill.
[c]Angiocath, Becton-Dickinson Vascular Access, Sandy, Utah.
[d]Passport DatascopeGas Module, Passport Corp, Paramus, NJ.
[e]Dinamap, Critikon, Tampa, Fla.
[f]Pulse oximeter, Nellcor, Calif.
[g]Cortisol-RIA, Diagnostic Products Corp, Los Angeles, Calif.
[h]Equitech Laboratory Inc, Alachua, Fla.

Appendix

Criteria used for behavioral pain scoring after ovariohysterectomy in dogs

Pain score	Behavioral signs
1 (minimal pain)	Relaxed, resting comfortably, not vocalizing, moving freely, calm or asleep, responds to calm voice and stroking with tail wagging
2 (faint pain)	Minimal agitation, resting calmly, barely noticeable alternation from signs of minimal pain, some position changes, responds to calm voice and stroking
3 (mild pain)	Mild agitation, some position changes, responds to calm voice and stroking, some salivation, occasionally vocalizing
4 (moderate pain)	Moderate agitation, vocalizing, excessive salivation, some vomiting, muscle trembling, frequent position changes, some thrashing movements, some response to calm voice and stroking
5 (severe pain)	Severe agitation, vomiting, defecation, vocalizing, excessive salivation, head tossing, violent thrashing movements, does not respond to calm voice and stroking, may require manual restraint to prevent self-injury

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