Postoperative analgesic effects of epidural administration of neostigmine alone or in combination with morphine in ovariohysterectomized dogs

Rodrigo L. Marucio, MV, MS; Stelio P. L. Luna, MV, PhD; Francisco J. Teixeira Neto, MV, PhD; Bruno W. Minto, MV, MS; Eduardo Hatschbach, MV, MS

**Objective**—To evaluate analgesic effects of epidurally administered neostigmine alone or in combination with morphine in dogs after ovariohysterectomy.

**Animals**—40 healthy bitches.

**Procedures**—After acepromazine premedication, anesthesia was induced. Dogs randomly received 1 of the following 4 epidural treatments 30 minutes before ovariohysterectomy (n = 10/group): saline (0.9% NaCl) solution (control), morphine (0.1 mg/kg), neostigmine (10 µg/kg), or morphine-neostigmine (0.1 mg/kg and 10 µg/kg, respectively). Analgesia was assessed for 24 hours after surgery by use of a visual analogue scale (VAS; scale of 0 to 10) or numeric descriptive scale (NDS; scale of 0 to 24) and by the need for supplemental analgesia (morphine [0.5 mg/kg, IM] administered when VAS was ≥ 4 or NDS was ≥ 8).

**Results**—Significantly more control dogs (n = 8) received supplemental analgesia, compared with the number of neostigmine-treated dogs (1); no dogs in the remaining groups received supplemental analgesia. Compared with values for the control dogs, the NDS scores were lower for morphine-neostigmine–treated dogs (from 2 to 6 hours and at 12 hours) and for morphine-treated dogs (all time points). The NDS scores were lower for morphine-treated dogs at 3, 12, and 24 hours, compared with values for neostigmine-treated dogs. The VAS was less sensitive than the NDS for detecting differences among groups.

**Conclusions and Clinical Relevance**—Epidurally administered neostigmine reduced the need for supplemental analgesia after ovariohysterectomy in dogs. However, analgesic effects were less pronounced than for epidurally administered morphine or morphine-neostigmine. Adding neostigmine to epidurally administered morphine did not potentiate opioid-induced analgesia. (Am J Vet Res 2008;69:854–860)

One of the most efficient alternatives for alleviating pain is epidural administration of analgesic drugs. When compared with results for the IM or IV routes of administration, epidural injection of analgesics, such as morphine, may result in a longer duration of analgesia with the use of lower dosages because drugs are administered in close proximity to the receptors that modulate the nociceptive pathway in the spinal cord. The goal when combining analgesic drugs administered into the epidural space is to achieve a synergistic analgesic effect via inhibition of nociception through various pathways.

Neostigmine is a cholinomimetic agent used in anesthesia for antagonizing the action of nondepolarizing neuromuscular blocking agents. This drug is devoid of neurotoxic effects when administered intrathecally to dogs and rats. In humans, there has been renewed interest in this drug because epidural administration of neostigmine in conjunction with other drugs (eg, lidocaine, bupivacaine, and morphine) substantially improves control of postoperative pain. Activation of muscarinic receptors located in the spinal cord is the mechanism probably responsible for analgesia induced by cholinomimetic agents such as neostigmine.

**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ETISO</td>
<td>End-tidal concentration of isoflurane</td>
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<tr>
<td>MAP</td>
<td>Mean arterial pressure</td>
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<tr>
<td>NDS</td>
<td>Numeric descriptive scale</td>
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<tr>
<td>PETCO₂</td>
<td>End-tidal partial pressure of carbon dioxide</td>
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<td>VAS</td>
<td>Visual analogue scale</td>
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From the Department of Veterinary Surgery and Anesthesiology, Faculdade de Medicina Veterinária e Zootecnia, Universidade Estadual Paulista, Botucatu, São Paulo, Brazil, 14870-000. Dr. Marucio’s present address is Rua Capitão Adão Pereira de Souza Cabral, 274, São Carlos, São Paulo, Brazil, CEP 13561-000. This manuscript represents a portion of a dissertation submitted by the first author to the Faculdade de Medicina de Botucatu, Universidade Estadual Paulista, for the Master of Science degree. Dr. Marucio was supported by a scholarship provided by the Conselho Nacional de Desenvolvimento Científico e Tecnológico. Presented in part at the 9th World Congress of Veterinary Anaesthesiology, Santos, Brazil, September 2006. The authors thank Dr. Luzia Trinca for statistical assistance. Address correspondence to Dr. Luna.
as neostigmine. More specifically, the mechanism for analgesia induced by cholinomimetic drugs primarily involves the activation of muscarinic type 1 receptors, although activation of nicotinic receptors may also be involved. Although intrathecal (subarachnoid) administration of neostigmine results in dose-dependent analgesia, the administration of neostigmine via this route has been virtually abandoned in humans because of a high incidence of vomiting and severe nausea. As an alternative to the intrathecal route, epidural administration of neostigmine can yield analgesia with a decreased incidence of adverse effects such as nausea and vomiting in humans undergoing orthopedic and obstetric procedures.

Analysis of data from humans suggests that neostigmine may have potential clinical application as an analgesic adjuvant to other drugs administered epidurally. The study reported here was conducted to evaluate the postoperative analgesic effects of epidural administration of neostigmine alone or in combination with morphine in bitches that underwent ovariolysterectomy.

Materials and Methods

Animals—Forty healthy client-owned adult bitches were selected for use in the study. Mean ± SD body weight was 13.7 ± 5.9 kg, and mean age was 16 ± 8 months. Health status was assessed on the basis that results of physical examination, CBC, and serum biochemical analysis (concentrations of BUN and creatinine and activities of alkaline phosphatase and alanine transaminase) were within reference ranges. Only dogs with calm and docile behavior that did not have evidence of discomfort or aversive reactions to palpation of the abdomen while interacting with the investigator during preoperative assessment were included in the study. The study was performed in accordance with the guidelines of the Brazilian College of Animal Experimentation and was approved by an institutional animal care committee (protocol No. 514 CEEA). Owner consent was obtained for each dog included in the study.

Anesthetic and presurgical procedures—Food and water were withheld from dogs for 12 and 6 hours before anesthesia, respectively. Acepromazine maleate (0.05 mg/kg, IM) was administered as a preanesthetic medication. Twenty minutes later, a 20-gauge catheter was inserted in a cephalic vein. Anesthesia was induced by administration of propofol (5 mg/kg, IV) 30 minutes after administration of acepromazine. The catheter was also used for fluid administration during anesthesia (lactated Ringer’s solution at a rate of 10 mL/kg/h). After endotracheal intubation, anesthesia was maintained with isoflurane in oxygen (50 to 100 mL/kg/min) by use of a circle breathing system. An adapter was inserted between the orotracheal tube and circle circuit to allow aspiration of gases for continuous measurement of ETISO and PETCO2. ISOFLO and PETCO2 by use of a multivariable monitor. Isoflurane vaporizer settings were adjusted to maintain surgical depth of anesthesia on the basis of clinical signs, whereas positive-pressure ventilation was instituted to maintain PETCO2 between 35 and 45 mm Hg throughout anesthesia.

Electrodes were affixed to the skin in accordance with a lead II ECG derivation to monitor heart rate, whereas a dorsal pedal artery or femoral artery was catheterized with a 20-gauge catheter connected to a fluid-filled pressure transducer system for recording MAP throughout anesthesia. Calibration (zero reference) for the pressure transducer was set at the level of the manubrium. Rectal temperature, recorded by the multivariable monitor via a rectal temperature probe, was maintained at > 37°C by means of a forced-air warming blanket and an electric heating pad.

Epidural treatments—After induction of anesthesia, dogs were positioned in sternal recumbency and the skin over the lumbosacral area was surgically prepared for aseptic insertion of a spinal needle into the lumbosacral epidural space. Correct needle placement was confirmed by the lack of CSF or blood at the needle hub and by a lack of resistance to the injection of 2 to 3 mL of air with a low-resistance syringe.

The study was randomized, placebo-controlled, and double-blinded. Dogs were assigned to 4 groups (10 dogs/group). The investigator who administered the epidural drugs and assessed postoperative pain (RLM) was unaware of the epidural treatment administered to each dog. Dogs in the control group received an epidural injection of saline (0.9% NaCl) solution (0.4 mL/kg).Preservative-free neostigmine sulfate (10 µg/kg) was administered to a second group, preservative-free morphine sulfate (0.1 mg/kg) was administered to a third group, and a combination of neostigmine and morphine (10 µg/kg and 0.1 mg/kg, respectively) was administered to the fourth group. In all treatment groups, final volume administered into the epidural space (0.4 mL/kg) was achieved by the addition of physiologic saline solution.

Doses of morphine and neostigmine selected for the study were determined on the basis of other reports. The dose of morphine (0.1 mg/kg) has been associated with negligible undesirable effects in dogs and reportedly results in postoperative analgesia that may last up to 12 hours. In human patients that underwent hysterectomy, coadministration of neostigmine (5 µg/kg) and bupivacaine as an epidural injection did not improve postoperative analgesia, compared with results for epidural administration of bupivacaine alone. However, coadministration of bupivacaine and a larger dose of neostigmine (10 µg/kg) prolonged the early postoperative analgesic effects of the bupivacaine.

After administration of epidural treatments, dogs were positioned in dorsal recumbency for 30 minutes before surgery commenced. Heart rate, MAP, ETISO, PETCO2, and rectal temperature were recorded at predefined intervals during anesthesia. Duration of surgery, length of abdominal incision, and variables recorded after discontinuation of the inhalant anesthetic (interval until first head lift and interval until standing) were recorded.

Surgical procedures—Bitches underwent routine ovariolysterectomy. An experienced surgeon (BWM) performed all surgeries, and a minimally invasive surgical technique was used. Duration of the surgical proce-
dure was consistent among dogs (approx 15 minutes). Traction and exposure of the ovaries was accomplished with a metallic hook, which enabled the surgeon to use a relatively short abdominal wall incision (3 cm), although the incision was lengthened slightly when necessary.

Assessment of postoperative analgesia—Postoperative analgesia was assessed subjectively by 1 investigator (RLM) at 1, 2, 3, 4, 6, 8, 12, and 24 hours after the end of anesthesia. The investigator was unaware of the epidural treatment administered to each dog. Two methods were used for assessment. A 10-cm horizontal line without graduation was used to determine the VAS score. The left end of the line indicated a total lack of pain, and the right end of the line indicated the strongest pain possible. The evaluator observed and interacted with each dog (eg, coaxing the dog and palpating the surgical incision) and then quantified the degree of pain by indicating a point on the VAS line. The distance between the point indicated by the evaluator and the left end of the horizontal line was measured to record the VAS score (in centimeters). The investigator also assessed postoperative analgesia in each dog by use of a descriptive scale modified from an NDS reported elsewhere (Appendix). The NDS contained 11 variables, and the sum of all variables could yield NDS values ranging from 0 to 24, where 0 represented a total lack of behavior indicative of pain and 24 represented behavior indicative of the most intense pain possible.

The interval until return of appetite was also evaluated by offering a meal (the same food that the dog was accustomed to eating at home). The interval elapsed by offering a meal (the same food that the dog was accustomed to eating at home). The interval elapsed by offering a meal (the same food that the dog was accustomed to eating at home). The interval elapsed by offering a meal (the same food that the dog was accustomed to eating at home). The interval elapsed by offering a meal (the same food that the dog was accustomed to eating at home). The interval elapsed by offering a meal (the same food that the dog was accustomed to eating at home).

Supplemental analgesia (ie, rescue analgesia) was performed with morphine (0.5 mg/kg, IM) when the VAS score was ≥ 4 cm or the NDS score was ≥ 8. Possible adverse reactions, such as emesis and other effects, were also recorded during the postoperative period.

Statistical analysis—Data were analyzed by use of a commercial software program. Quantitative variables were compared by use of an ANOVA followed by a Tukey method for multiple comparisons. Qualitative variables (eg, number of dogs requiring rescue analgesia in each treatment group) were compared by use of a χ² or Fisher exact test. A Friedman test was used to compare scores within each group, whereas a Kruskal-Wallis test followed by a Dunn test was used to compare scores among treatment groups. Unless otherwise stated, psychologic variables were reported as mean ± SEM, whereas scores were reported as median and range of values. Significance was set at values of P < 0.05.

Results

Demographic data and variables recorded during anesthesia and recovery from anesthesia—No significant differences were detected among treatment groups with regard to age, body weight, and variables recorded during anesthesia (duration of surgery, length of surgical incision, heart rate, MAP, P Etco₂, P Etso₂, and rectal temperature). Anesthesia recovery characteristics (interval until first head lift and interval until standing) were also similar among treatment groups (Table 1). Two dogs receiving neostigmine and 1 dog receiving morphine had an episode of emesis after anesthesia was discontinued.

Assessment of postoperative pain—Significantly more control dogs (n = 8) received supplemental opioid analgesia during the first 4 hours after anesthesia because of a VAS score ≥ 4 or NDS score ≥ 8 than did neostigmine-treated dogs (1). Of the 8 control dogs that received supplemental morphine, 7 received analgesic supplementation only 1 time (from 1 until 4 hours after surgery), whereas 1 dog received analgesic supplementation 2 times (1 and 2 hours after surgery). At 2 hours after surgery, supplemental analgesia was administered to 1 dog treated epidurally with neostigmine, whereas no supplemental analgesia was required throughout the observation period in dogs treated with epidural administration of morphine or the combination of morphine and neostigmine.

The highest VAS scores were recorded 2 hours after surgery in the control group (median, 2.9; range, 0 to 4 or NDS score < 8 than did neostigmine-treated dogs (1). Of the 8 control dogs that received supplemental morphine, 7 received analgesic supplementation only 1 time (from 1 until 4 hours after surgery), whereas 1 dog received analgesic supplementation 2 times (1 and 2 hours after surgery). At 2 hours after surgery, supplemental analgesia was administered to 1 dog treated epidurally with neostigmine, whereas no supplemental analgesia was required throughout the observation period in dogs treated with epidural administration of morphine or the combination of morphine and neostigmine.

The highest VAS scores were recorded 2 hours after surgery in the control group (median, 2.9; range, 0 to 2.2).

Table 1—Mean ± SEM values for demographic data and variables recorded during anesthesia and recovery from anesthesia in 40 bitches premedicated with acepromazine and anesthetized with isoflurane that underwent ovariohysterectomy after epidural administration of 1 of 4 treatments (10 dogs/group).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Neostigmine</th>
<th>Morphine</th>
<th>Morphine-neostigmine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>13.5 ± 2.2</td>
<td>13.2 ± 1.3</td>
<td>13.7 ± 1.7</td>
<td>14.3 ± 2.3</td>
</tr>
<tr>
<td>Age (mo)</td>
<td>16 ± 2</td>
<td>17 ± 3</td>
<td>16 ± 3</td>
<td>15 ± 3</td>
</tr>
<tr>
<td>Length of abdominal incision (cm)</td>
<td>3.0 ± 0</td>
<td>3.6 ± 0.6</td>
<td>3.0 ± 0.1</td>
<td>3.3 ± 0.2</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>15 ± 1</td>
<td>15 ± 2</td>
<td>15 ± 2</td>
<td>15 ± 1</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>100 ± 3</td>
<td>102 ± 2</td>
<td>94 ± 3</td>
<td>97 ± 3</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>78 ± 3</td>
<td>78 ± 3</td>
<td>74 ± 3</td>
<td>78 ± 4</td>
</tr>
<tr>
<td>P Etso₂ (%)</td>
<td>1.44 ± 0.04</td>
<td>1.39 ± 0.05</td>
<td>1.35 ± 0.04</td>
<td>1.37 ± 0.04</td>
</tr>
<tr>
<td>P Etco₂ (mm Hg)</td>
<td>42 ± 1</td>
<td>42 ± 1</td>
<td>40 ± 1</td>
<td>41 ± 1</td>
</tr>
<tr>
<td>Rectal temperature (°C)</td>
<td>37.3 ± 0.1</td>
<td>37.2 ± 0.1</td>
<td>37.2 ± 0.1</td>
<td>37.0 ± 0.1</td>
</tr>
<tr>
<td>Interval until first head lift (min)*</td>
<td>20 ± 5</td>
<td>14 ± 3</td>
<td>24 ± 3</td>
<td>20 ± 4</td>
</tr>
<tr>
<td>Interval until standing (min)*</td>
<td>45 ± 12</td>
<td>59 ± 20</td>
<td>53 ± 15</td>
<td>84 ± 16</td>
</tr>
</tbody>
</table>

Epidural treatments were saline (0.9% NaCl) solution (0.4 mL/kg) for the control group, neostigmine (10 µg/kg), morphine (0.1 mg/kg), and a combination of neostigmine and morphine (10 µg/kg and 0.1 mg/kg, respectively). *Represents interval from discontinuation of inhalant anesthetic administration until event.
The highest median value for NDS was recorded 2 hours after surgery in the control group (median, 7; range, 1–8) and was significantly lower (P < 0.05; Dunn test) from the value for neostigmine. In comparison to the control group, NDS values for dogs receiving morphine (3.1 ± 0.3 hours), morphine-neostigmine (3.2 ± 0.4 hours), or neostigmine (8.5 ± 8.3 hours) were homogenous among treatment groups. Another study was likely reduced because demographic data (age, sex, weight, and body condition score) were homogenous among treatment groups. Another possible confounder that may cause bias in experiments that compare the efficacy of drugs for alleviating postoperative pain is the type of surgery. Variability among dogs of the same surgical procedure (ovariohysterectomy) may not be sufficient to allow detection of a possible benefit that may have been achieved by adding neostigmine to morphine.

In this study, the subjective nature of the clinical assessment of postoperative pain and the considerable variability that may exist among animals in terms of response to pain,14 we sought to standardize the study population on the basis of physical and laboratory assessments and also on the basis of behavior and interaction with the individual responsible for evaluating postoperative pain. Variability among dogs of the study was likely reduced because demographic data were homogenous among treatment groups. Another possible confounder that may cause bias in experiments that compare the efficacy of drugs for alleviating postoperative pain is the type of surgery and amount of tissue trauma.13 Because variations in the amount of surgical trauma may result in differences in the intensity of nociception,15 the same experienced surgeon performed all surgeries by use of the same surgical technique to provide similar amounts of tissue trauma in all treatment groups.

Table 2—Median (range) scores of pain assessment for the VAS and NDS recorded during the postoperative period in 40 bitches medicated with acepromazine and anesthetized with isoflurane that underwent ovariohysterectomy after epidural administration of 1 of 4 treatments (10 dogs/group).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment group</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS</td>
<td>Control</td>
<td>2.5 (0–4.1)</td>
<td>2.9 (0–4.1)</td>
<td>1.5 (0–3.0)</td>
<td>0.5 (0–3.6)</td>
<td>0.5 (0–3.4)</td>
<td>0 (0–3.8)</td>
<td>0 (0–2.1)</td>
<td>0 (0–1.0)</td>
</tr>
<tr>
<td></td>
<td>Neostigmine</td>
<td>0.8 (0–3.1)</td>
<td>1.0 (0–4.2)</td>
<td>0.5 (0–2.5)</td>
<td>0.5 (0–2.5)</td>
<td>0 (0–2.5)</td>
<td>0 (0–3.5)</td>
<td>0 (0–2.5)</td>
<td>0 (0–2.5)</td>
</tr>
<tr>
<td></td>
<td>Morphine</td>
<td>0 (0–1.6)</td>
<td>0* (0–0.8)</td>
<td>0 (0–1.5)</td>
<td>0 (0–6)</td>
<td>0 (0–1.2)</td>
<td>0 (0–6)</td>
<td>0 (0–6)</td>
<td>0 (0–6)</td>
</tr>
<tr>
<td></td>
<td>Morphine-neostigmine</td>
<td>0* (0–1.6)</td>
<td>0* (0–1.0)</td>
<td>0 (0–1.0)</td>
<td>0 (0–6)</td>
<td>0 (0–1.2)</td>
<td>0 (0–6)</td>
<td>0 (0–6)</td>
<td>0 (0–6)</td>
</tr>
</tbody>
</table>

| NDS      | Control         | 7 (1–8) | 7 (4–10) | 5.5 (2–9) | 4.5 (2–9) | 5 (2–7) | 5 (0–7) | 4 (1–5) | 1.5 (0–3) |
|          | Neostigmine     | 4 (3–7) | 4 (1–9) | 4.5 (2–6) | 4 (0–7) | 3.5 (0–7) | 2.5 (1–6) | 3 (1–7) | 2 (0–4) |
|          | Morphine        | 2.5* (1–5) | 2* (0–5) | 1* (1–0) | 1* (0–4) | 1* (0–4) | 1* (0–3) | 1* (0–3) | 1* (0–3) |
|          | Morphine-neostigmine | 4 (1–6) | 2.5* (0–7) | 1* (0–6) | 1.5* (0–5) | 1* (1–6) | 1.5 (0–5) | 1.5* (0–3) | 1 (0–3) |

*Within a column within a variable, value differs significantly (P < 0.05; Dunn test) from the value for the control group. †Within a column within a variable, value differs significantly (P < 0.05; Dunn test) from the value for neostigmine.
See Table 1 for remainder of key.
Although quantitative variables, such as an increase in heart rate and blood pressure, have been used for the assessment of pain in animals, these variables are influenced by a wide array of nonpainful conditions that may limit their diagnostic value. Behavioral changes, although effective for assessing pain in many instances, may also vary considerably among animals and may be altered in hospitalized patients. To our knowledge, there is no single method that has been proven to be optimally effective for the clinical assessment of postoperative pain. Therefore, a combination of a VAS and NDS was used in an attempt to provide the best assessment of postoperative pain. On the basis of the results of the study reported here, the NDS was more effective than the VAS for use in detecting the need for supplemental analgesia. For the 9 supplemental analgesic interventions in the control group (7 dogs received 1 supplemental intervention each, and 1 dog received 2 supplemental interventions), supplemental analgesic was administered on the basis that only the NDS score was above the threshold (≥ 8) for 6 assessments. In the control group, supplemental morphine was administered when only the VAS score was above the threshold (i.e., ≥ 4) for 1 assessment and when both the VAS and NDS scores were above the respective thresholds for another 2 assessments.

The use of supplemental analgesics for treating animals with unacceptable signs of pain is a confounding factor and may mask the evaluation of the effectiveness of an original analgesic treatment. Therefore, the VAS and NDS scores reported here should be analyzed with the caveat that both scoring systems were influenced by the use of supplemental analgesia (0.5 mg/kg of morphine, IM) during the early postoperative period in 8 control dogs and 1 dog that received neostigmine. Given the relatively large number of control dogs that received supplemental analgesia, it is likely that had none of the control dogs received supplemental analgesia, pain scores would have been higher in this group and the differences in severity of pain between the control and other treatment groups would have been more evident. However, for humane reasons, pain studies that do not incorporate a plan for rescue analgesia are not acceptable.

Although the use of supplemental opioid analgesia in 8 of 10 control dogs made it more difficult to evaluate the analgesic efficacy of the epidural treatments, a difference between the control and other treatment groups was still detected by use of the VAS and NDS. On the basis of the results for both scoring systems, epidural administration of morphine and morphine-neostigmine provided the best analgesic effect that was evident mainly during the early postoperative period (up to 6 to 8 hours after termination of surgery and anesthesia). An alternative to dealing with the masking effect of rescue analgesia on the evaluation of efficacy of an analgesic treatment is to compare the number of animals that receive rescue analgesics or the number of rescue analgesic interventions required in each treatment group. Although the analgesic effects of epidural administration of neostigmine were inferior to those after epidural administration of morphine or morphine-neostigmine, the use of neostigmine alone still resulted in an analgesic effect because fewer dogs in that treatment group received supplemental opioid analgesia in comparison with the number of control dogs requiring supplemental analgesia.

Assessment of the interval until the return of appetite during the postoperative period may provide an inverse correlation with the degree of patient comfort, and an earlier return of appetite may be expected in pain-free animals. This variable was significantly delayed in control dogs, compared with results for the other treatment groups, and this result could be interpreted as a clinical sign of patient discomfort or pain. However, the sedative effects caused by the use of supplemental morphine during the early postoperative period in 8 of 10 control dogs may have represented a confounding factor for this variable.

In another study, investigators reported that the use of 1 to 4 µg of neostigmine/kg administered via the epidural route in combination with lidocaine resulted in dose-dependent analgesia in human patients who underwent minor orthopedic procedures. Another study involving the addition of 5 and 10 µg of neostigmine/kg to bupivacaine for epidural administration prior to hysterectomy in humans revealed that only the dose of 10 µg/kg resulted in significant postoperative analgesia, compared with results for the use of bupivacaine alone. However, the apparent discrepancy in the dose of neostigmine that provided effective analgesia in that study may have been related to the greater analgesic effectiveness of epidural administration of neostigmine for somatic pain, rather than for visceral pain. Evidence that supports this viewpoint was obtained in a study in which intrathecal administration of neostigmine was more effective for alleviation of somatic pain (vaginoplasty) than for alleviation of visceral pain (tubal ligation) in women. The dose of neostigmine (10 µg/kg) in the study reported here was determined on the basis of the dose recommended for hysterectomy in humans.

Antinociceptive effects of neostigmine may be more intense in female than in male subjects. Evidence for a sex-related difference in the antinociceptive efficacy of this drug was obtained in a study in mice in which neostigmine was 5 times as potent for the relief of pain in female mice as it was in male mice. Spinal analgesia induced by neostigmine is related to an increase in acetylcholine concentrations within the spinal cord, which stimulates muscarinic and nicotinic cholinergic receptors. A greater concentration of nicotinic receptors has been identified in the spinal cord of female mice, and this difference in receptor population may explain the greater analgesic efficacy in females.

In humans, subarachnoid (intrathecal) administration of neostigmine is associated with a higher incidence of vomiting and nausea during the postoperative period, compared with results after epidural administration of neostigmine. Emesis is believed to be secondary to rostral diffusion of drugs via the CSF after intrathecal administration, and epidural administration of neostigmine reduces the incidence of this effect in humans. Volting was recorded during the postoperative period, only 2 dogs from the neostigmine group and 1
dog from the morphine group vomited, and vomiting did not result in further complications.

Epidural administration of neostigmine provided a moderate postoperative analgesic effect in most female dogs that underwent ovariohysterectomy in the study reported here. Analgesia induced by epidural administration of neostigmine was less, compared with the analgesia induced by epidural administration of morphine or morphine combined with neostigmine. In dogs with postoperative pain as a result of ovariohysterectomy, the addition of neostigmine to morphine did not potentiate the analgesic effects of the opioid. Because neostigmine may have a role as an adjuvant for pain control when combined with other analgesics for epidural administration, additional studies are needed to assess whether neostigmine improves the postoperative analgesia provided by drugs administered via the epidural route for dogs with postoperative pain resulting from other types of surgical procedures.

References


Appendix appears on next page
Appendix

Modified criteria\(^{14}\) for the NDS for assessment of pain in dogs after ovariohysterectomy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>≤ 10% above value recorded before surgery</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt; 10% to 30% above value recorded before surgery</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt; 30% to 50% above value recorded before surgery</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&gt; 50% above value recorded before surgery</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory pattern</td>
<td>Thoracoabdominal movement</td>
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<td>Moderate abdominal movement</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Marked abdominal movement</td>
<td>2</td>
</tr>
<tr>
<td>Rectal temperature</td>
<td>Within reference range</td>
<td>0</td>
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<tr>
<td></td>
<td>Greater than reference range</td>
<td>1</td>
</tr>
<tr>
<td>Salivation</td>
<td>Typical amounts of saliva</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Excessive amounts of saliva</td>
<td>1</td>
</tr>
<tr>
<td>Appearance</td>
<td>Typical</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Mild changes (eyelids partially closed; ears flattened or abnormal carriage)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Moderate changes (eyes sunken or glazed; unthrifty)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Severe changes (eyes pale; large pupils; grimace or other abnormal facial expressions; protective posture; hunched-back position; abnormal limb position; grunting before expiration; teeth grinding)</td>
<td>3</td>
</tr>
<tr>
<td>Comfort</td>
<td>Calm, awake, and interested in surroundings</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Awake but not interested in surroundings</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Extremely agitated or thrashing</td>
<td>2</td>
</tr>
<tr>
<td>Behavior without interaction</td>
<td>Typical behavior, interested in surroundings</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Minor changes, less interested in surroundings than usual</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Moderately abnormal (less mobile and less alert than usual; unaware of surroundings; extremely restless)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Markedly abnormal (extremely restless; vocalization; self-mutilation; groaning; facing the back of the cage)</td>
<td>3</td>
</tr>
<tr>
<td>Behavior in response to manipulation of surgical incision</td>
<td>No aversive behavior</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Minimal aversive behavior, pulls away when surgical site is touched, and turns head to look at surgical incision</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Vocalizes and turns head to look at surgical incision</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Violent reactions to stimuli; vocalizing; growling when approached; snapping; extremely restless; will not move when coaxed</td>
<td>3</td>
</tr>
<tr>
<td>Vocalization</td>
<td>Quiet</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Vocalization that can be interrupted by calmly speaking to dog and petting</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Intermittent vocalization or whimpering; no response to calmly speaking to dog and petting</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Continuous vocalization that is abnormal for the specific dog</td>
<td>3</td>
</tr>
<tr>
<td>Movement</td>
<td>Typical amount of movement</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Frequent position changes or reluctance to move</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Thrashing</td>
<td>2</td>
</tr>
<tr>
<td>Pupil size</td>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Large</td>
<td>1</td>
</tr>
</tbody>
</table>