Evaluation of Topical Epidural Morphine for Postoperative Analgesia Following Hemilaminectomy in Dogs

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**Clinical Relevance**

A randomized prospective study was conducted in dogs undergoing hemilaminectomy procedures for Hansen type I disk protrusion to compare postoperative analgesia achieved with topical spinal application of morphine versus saline. An absorbable gelatin sponge was placed in the defect next to the dura and soaked with either preservative-free morphine (0.1 mg/kg) or saline (0.1 ml/kg) just before wound closure. For 48 hours after surgery, dogs were monitored for pain using visual analog and numeric descriptive scales and given rescue analgesia according to study guidelines. A Kaplan–Meier survival analysis revealed that dogs in the morphine group had a longer (13.3 ± 3.6 hours) duration of postoperative analgesia than those in the control saline group (5.3 ± 1.8 hours), and dogs in the morphine group also required fewer doses of additional pain medication. Preservative-free morphine administered topically via an absorbable gelatin sponge appears to be a promising method to alleviate postoperative pain in dogs undergoing hemilaminectomy procedures.

**Introduction**

Dogs presenting with intervertebral disk herniation are usually in pain during examination.

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Injury to the spinal cord and nerve roots from extradural compression results in swelling, ischemia, and hemorrhage, which in turn leads to persistent or intermittent somatic or visceral neuropathic pain.\textsuperscript{1} To alleviate spinal cord com-
provision, hemilaminectomy procedures are performed to remove the extruded disk material and provide adequate space for additional spinal cord swelling. Postoperative pain is usually severe for dogs undergoing hemilaminectomy. Hemilaminectomy postoperative pain is a typical nociceptive pain initiated and sustained by chemical mediators of inflammation. Opioids such as morphine are frequently used for alleviating this type of postoperative pain and can be given as single injections or as constant rate infusions (CRIIs), often in combination with other drugs. Systemic administration of opioids provides a relatively short duration of analgesia, making frequent readministration necessary. For example, a single IM injection of morphine provides approximately 3 to 5 hours of analgesia. For this reason, CRI is used to provide a continuous level of analgesia; it can also be readily titrated to achieve the desired effect. An IV catheter, a syringe pump (ideally), and constant monitoring for catheter patency are required. Side effects associated with systemic morphine administration in dogs include bradycardia, nausea, vomiting, reduction of gastrointestinal motility, histamine release, and pupillary constriction.

Traditional epidural administration of opioid drugs involves either an epidural injection or placement of an epidural catheter when prolonged administration of analgesics is necessary. Epidural administration provides an alternative route for postoperative pain management in animals undergoing surgery, especially of the abdomen and pelvic limbs. In contrast to systemic morphine administration, the epidural route provides the advantage of a longer duration of analgesia with less cardiorespiratory depression. Although epidural administration of morphine is relatively easy to perform and obviously effective for treating postoperative pain in dogs undergoing hindquarter surgery, its use is complicated in spinal surgery if diagnostic imaging with contrast media placed in the subarachnoid space is needed before surgery. To induce analgesia after epidural administration, morphine must move from the epidural space; cross the dura mater; and diffuse through the arachnoid, subarachnoid space, and cerebrospinal fluid (CSF) to reach the spinal cord to take action. Because of its low lipophilicity, morphine remains in the CSF for a long period. The effect of CSF collection, imaging procedures, and myelography on the analgesic effectiveness of epidural morphine is unknown.

Topical application of such analgesic agents as preservative-free morphine periepidurally (to the dura mater of the spinal cord) during a hemilaminectomy procedure in dogs is a novel idea. Several groups have investigated topical epidural application of morphine with various carriers and other drugs in humans undergoing spinal surgery. In 1995, a preliminary clinical study in 45 people undergoing lumbar disectomy investigated the combination of methylprednisolone and morphine delivered via an absorbable gelatin sponge (Gelfoam, Pfizer) at the time of surgery. These authors were able to discharge patients on the first day after surgery, and minimal analgesics were required. Morphine nerve paste was evaluated for postoperative pain control after laminectomy pro-

In contrast to systemic morphine administration, the epidural route provides the advantage of longer duration of analgesia with less cardiorespiratory depression.
cedures, and the study showed that it reduced narcotic drug consumption in the postoperative period and was apparently safe. Later, however, it was demonstrated that the use of the paste may increase the risk for postoperative wound infection. In 2002, Chen reported on topical microfibrillar collagen (Avitene, Davol, Warwick, RI) mixed with methylprednisolone and morphine in 80 patients undergoing lumbar laminectomy. In that study, the author concluded that epidural administration of this product appeared beneficial in that patients required less postoperative analgesia. Morphine was delivered via an absorbable carbohydrate product (Adcon-L, Gliatech, Inc.) that was marketed in 2002 as an adhesion barrier to prevent epidural fibrosis during microdiskectomy procedures. In another study, the investigators used Oxiplex/SP gel (FzioMed, San Luis Obispo, CA), an absorbable product made from polyethylene oxide, sodium carboxymethylcellulose, and calcium chloride, as a carrier for morphine. The combination was effective for 36 hours after administration, and there were no complications. Most recently, some of the same investigators conducted a preliminary study to evaluate the use of a petroleum jelly–sterile oil–morphine compound as both an adhesion prevention agent and a carrier for morphine.

Absorbable gelatin sponges are frequently used during hemilaminectomy procedures for hemostasis at the surgical site and then removed before closure. Although not labeled for this indication, gelatin sponges have compared favorably with other methods for prevention of epidural scar tissue following lumbar laminectomy in dogs. The delivery of morphine via an absorbable gelatin sponge offers precise topical application of morphine on the anatomic site via direct visualization and potentially retains the morphine at the surgical site for sustained analgesic delivery. Topical application to the epidural tissues at the surgical site could potentially avoid side effects of respiratory depression that may occur with intravenous and other systemic administration of morphine.

Given the background in the human literature, we wished to evaluate the topical application of morphine peripherally to the spinal cord in dogs undergoing hemilaminectomy procedures for Hansen type I disk disease. We hypothesized that the delivery of morphine in an absorbable gelatin sponge would provide satisfactory postoperative analgesia with minimal complications. The objectives of this feasibility study were to compare the analgesic duration of topical epidural administration of morphine with the effect of physiologic saline delivered in an absorbable gelatin sponge and assess any potential side effects associated with the delivery of topical morphine in dogs undergoing hemilaminectomy procedures.

**Topical application of preservative-free morphine peripherally on the spinal cord during a hemilaminectomy procedure in dogs is a novel idea.**

**MATERIALS AND METHODS**

**Animals and Study Design**

The study was approved by the Animal Care and Use Committee of Veterinary Specialty Center of Indiana, and signed informed client consent was obtained from the dogs’ owners. Dogs with behavioral issues that precluded fre-
quent examination or those with lack of deep pain sensation were excluded. Twelve dogs with Hansen type I disk extrusion (confirmed via computed tomography [CT] and/or myelography) were enrolled in the study. All dogs underwent physical and neurologic examinations, and routine complete blood counts and blood chemistry analyses were conducted on all dogs. The neurologic examination evaluated cranial nerves, forelimb reflexes, pelvic limb reflexes, perineal reflex, panniculus reflex, pain on palpation of the vertebral spinous processes, ambulation status, muscle tone to the extremities, motor function to extremities, and conscious proprioception. The degree of neurologic impairment was then classified into one of four groups: ataxia, ambulatory paraparesis, nonambulatory paraparesis, or paraplegia. Study dogs were randomly assigned to one of two treatment groups. Group one dogs (n = 6) were assigned to receive preservative-free morphine (Dumorph, Elkins-Sinn, Cherry Hill, NJ) at 0.1 mg/kg [0.045 mg/lb], and group two dogs (n = 6) were assigned to receive the same volume of physiologic saline applied at the time of surgery.

The mean time to first rescue was **13.3 hours for the morphine group and 5.3 hours for the saline control group.**

Anesthesia, Imaging, and Surgical Protocol

All dogs received the routine anesthetic and intraoperative pain management protocols for this type of surgery at the Veterinary Specialty Center of Indiana. Dogs were premedicated with hydromorphone (Baxter; 0.05 mg/kg [0.023 mg/lb] IM) and acepromazine (Aceproject, Butler Animal Health Supply; 0.1 mg/kg [0.045 mg/lb] IM). After 20 minutes, an IV catheter was placed and animals were induced to anesthesia with tiletamine–zolazepam (Telazol, Fort Dodge Animal Health; 2.2 mg/kg [1 mg/lb] IV). The dogs were then intubated and maintained with isoflurane (Attrane, Minrad, Orchard Park, NY) in 100% oxygen.

All dogs were transferred to radiology and underwent CT examination (GE Healthcare model number 2200290) to assist in locating the site of extradural compression. If the site was identified, the animals were immediately taken to surgery. If localization of extradural compression was uncertain, myelography and a repeat CT scan were conducted to localize the lesion, and the animal was then transferred to surgery.

Once the animals were in the operating room, a loading dose of morphine sulfate (Baxter; 0.5 mg/kg [0.23 mg/lb] IV) and ketamine (Fort Dodge Animal Health; 0.6 mg/kg [0.27 mg/lb] IV) was administered, and a CRI with morphine (0.6 mg/kg/hr [0.27 mg/lb/hr]) and ketamine (0.6 mg/kg/hr [0.27 mg/lb/hr]) in a balanced electrolyte solution (lactated Ringer’s solution, Butler Animal Health Supply) was begun. All dogs were monitored during general anesthesia via electrocardiography, noninvasive blood pressure measurement, esophageal thermometer, and pulse oximeter. Cefazolin (Faulding Pharmaceutical, Elizabeth, NJ; 22 mg/kg [10 mg/lb] IV) was administered at anesthetic induction and again 2 hours later.

A hemilaminectomy procedure to provide surgical decompression and allow removal of the nucleus pulposus in the spinal canal was performed by one of two surgeons. Gelfoam was then cut to fit the hemilaminectomy win-
A. P. Wehrenberg, L. Freeman, J. C. Ko, M. E. Payton, and R. E. Spivack

dow in the vertebral body next to the dura mater of the spinal cord. The sponge was placed in direct contact with the spinal cord. Immediately after the sponge was placed on the surgical site, the treatment solution (either 0.1 mg/kg [0.045 mg/lb] of preservative-free morphine or 0.1 ml/kg [0.045 ml/lb] of physiological saline) was applied directly to the sponge using a syringe and needle. Closure of the surgical site was routine using absorbable polydioxanone sutures for fascia and staples for the skin.

After surgery, the dogs were transferred to an intensive care setting for recovery and postoperative care, including monitoring for pain and assessment of cardiopulmonary function. The morphine–ketamine CRI was discontinued, the animals were extubated, and assessment of postoperative pain began (time 0).

Postoperative Assessment
Each animal was evaluated every 2 hours for a 48-hour period beginning at extubation. Animals were assessed for body temperature, heart and respiratory rates, and pain. All observations were made by four trained individuals who were masked to treatment group, routinely worked in the intensive care unit, and were familiar with the two pain assessment systems used in this study.

The numeric descriptive scale (NDS) consisted of five categories (demeanor, comfort, vocalization, posture, and response to touch), with each category being ranked on a scale of 0 to 20. The scores for each category were summed to determine the total NDS score for each animal (see box on page E6). A visual analog scale (VAS)—a 0 to 100 scale in which 0 indicated a total lack of pain and 100 indicated the most intense pain possible (characterized by such signs as extreme vocalization, inability to be approached, and thrashing)—was also used to assess pain.

Rescue Analgesia
Before the study, it was determined that when a dog reached a total score of 20 in either pain scoring system, it would be considered to be in pain and rescue morphine (0.5 mg/kg [0.23 mg/lb] slow IV) would be given. The time was recorded as the time to first rescue. After this, pain assessments were continued at 2-hour intervals and additional rescue doses of morphine were administered as necessary, but not more often than every 6 hours unless the attending surgeon was consulted about the patient’s condition. The time and number of rescue doses for each animal were recorded. All dogs were treated humanely; if at any time a question arose about pain or the overall care of the patient, the attending surgeon was consulted and appropriate care provided. No additional analgesics or NSAIDs were administered.

After 48 hours, dogs were released for discharge from the hospital when the attending surgeon deemed it appropriate. Before discharge, a neurologic examination was performed. The animals were reevaluated 2 and 8 weeks after surgery, and a neurologic examination was performed at each follow-up visit to monitor return of neurologic function.

Statistical Analysis
Heart rates, respiratory rates, body temperatures, and the NDS and VAS pain assessment scores were analyzed using analysis of variance with significance set at $P \leq .05$. The Kaplan–
Pain Assessment Parameters for Numeric Descriptive Scale and Visual Analog Scale in Dogs

NUMERIC DESCRIPTIVE SCALE

Demeanor (i.e., aggressiveness, signs of depression, disinterest, and nervousness)
- Quiet = 0
- Content = 0
- Bouncy = 0

Comfort (i.e., restlessness)
- Comfortable = 0

Vocalization (i.e., crying, groaning, screaming)
- Not vocalizing = 0

Posture (i.e., rigid, hunched)
- Normal = 0

Response to touch (i.e., crying, flinching, snapping, growling)
- None = 0

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VISUAL ANALOG SCALE

- 0 ___________________________________________________________________________ 100
- No pain
- Extreme pain*

*For example, a dog in extreme pain might be depressed; have a hunched posture or rigid muscle tone; be restless; cry, whimper, or scream when touched; and/or be aggressive.

*Range, 0 (normal or none) to 20 (most severe) for each main category.

Meier survival tool was used to compare the number of dogs requiring rescue analgesia (morphine) and the time of administration of the first rescue dose.

RESULTS

The study was conducted from May to December 2008. Twelve dogs were enrolled in the study, with six in each group. There were
no significant differences in the two groups in breed, body weight, gender, preoperative neurologic status, or preoperative pain scores (Table 1). Four of the dogs in the control group exhibited clinical signs for 4 weeks or more before presentation compared with none in the treatment group. Five dogs in the control group and two in the morphine group required myelography in addition to CT scans for localization of the compression site. All of the lesions were located between T10 and L3, with no significant differences between groups.

Each surgery took approximately 1 hour.

The time and frequency of rescue morphine administration in each dog (by group) are presented in Table 2. Three of six (50%) dogs in the control group required rescue morphine at 2 hours and another dog required rescue morphine at 4 hours (Table 2). In contrast, two of six dogs in the morphine group (33%) required rescue morphine at 6 hours (Table 2). The rest of the animals in the morphine group did not require postoperative rescue for pain until at least 14 hours (Table 2). The saline-treated dogs required significantly \( P < 0.01 \) more frequent rescue for pain than the morphine-treated dogs.

The results of this study support the hypothesis that topical application of morphine periepidurally via the gelatin sponge provided a postoperative analgesic effect in dogs undergoing a hemilaminectomy procedure.

The average dose of morphine–ketamine CRI given to each dog was 0.6 mg/kg/hr [0.27 mg/lb/hr]. The average vaporizer setting for isoflurane was between 1.5% and 1.75%. There were no surgical complications or excessive bleeding noted during or after surgery. All of the dogs had surgical lesions typical of disk extrusions (Hansen type I), confirming the site indicated on preoperative diagnostic imaging. Durotomy was not performed on any animal.

The mean \((\pm SD)\) duration of analgesia from extubation to the first administration of postoperative rescue pain medication was 13.3 \((\pm 3.6)\) hours for the morphine group and 5.3 \((\pm 1.8)\) hours for the saline control group \(( P < 0.01 \) ). The Kaplan–Meier survival analysis demonstrated a significant \(( P < 0.01 \) ) difference between groups, with more dogs in the morphine group surviving a longer time without rescue analgesia in the postoperative period than in saline group (Figure 1).

Heart rates ranged from 87 to 128 bpm for the control group and 96 to 119 bpm for the morphine group. Respiratory rates for all dogs ranged between 19 and 34 breaths/min. Body temperatures for all dogs ranged between 97.1°F and 102.3°F. There were no statistically significant differences in heart rate, respiratory rate, or body temperature between groups. Bradycardia, vomiting, respiratory depression, urine retention, and superficial or deep wound infection were not observed in any of the dogs in this study.

Two of the dogs in the saline group and three dogs in the morphine group had normal ambulation and resolution of neurologic signs by 2 weeks. All of the dogs in this study returned to being ambulatory within 8 weeks of their surgery. There were no significant differences between groups in return of neurologic function or return to ambulation. No postoperative complications were recorded except in one dog.
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<td>Normal ambulation and resolution of clinical signs at 8-wk follow-up examination (n = 3)</td>
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One animal in the morphine group recovered from the surgery within 2 weeks and was ambulatory. At 4 weeks, the animal again presented with clinical signs of pain and neurologic dysfunction of the pelvic limbs. A CT scan revealed further extrusion of disk material into the spinal canal at the site of the previous surgery. Exploratory surgery was performed; the Gelfoam was not found and apparently had already been absorbed. A thin fibrous portion of tissue covered the hemilaminectomy window. This tissue was removed, and the extruded disk material was retrieved from the spinal canal. The animal made a full recovery (ambulatory and pain free). For study purposes, only the initial procedure was included in the trial.

**DISCUSSION**

The results of this study support the hypothesis that topical application of morphine periepidurally via a gelatin sponge provides a postoperative analgesic effect in dogs undergoing a hemilaminectomy procedure. This was demonstrated by the longer duration of analgesia as characterized by the time to the first dose of rescue morphine and the less frequent requirement for rescue pain medication in the first 48 hours in the morphine group compared with the saline control group.

In this study, the dogs in both groups were premedicated with acepromazine–hydromorphone,

![Figure 1. Kaplan–Meier survival analysis of dogs treated with morphine (0.1 mg/kg; n = 6) versus the same volume (0.1 ml/kg) of saline (control; n = 6) over 48 hours after surgery. The y-axis represents the percentage of dogs surviving without rescue pain medication; the x-axis represents the 48-hour postoperative period. Most of the animals in the saline control group had already received rescue analgesia when compared with animals in the morphine treatment group at any given time. Plots are significantly different (P ≤ .05).](image)

**TABLE 2. Time and Frequency of Administration of Rescue Pain Medication in the Control (0.1 ml/kg saline) and Morphine (0.1 mg/kg) Treatment Groups**

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<th>Group</th>
<th>Time (hr) of Rescue Morphine†</th>
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*Saline-treated dogs required significantly (P < .01) more frequent rescue for pain than the morphine-treated dogs.
†Time 0 = time of extubation.
induced with tiletamine–zolazepam, and subsequently given a CRI of morphine–ketamine during surgery as part of the routine anesthetic–pain-management protocol used at the Veterinary Specialty Center of Indiana. The opioid premedication and intraoperative CRI of analgesic agents likely extended the duration of analgesia in some dogs, as demonstrated in the saline control group, which had a mean duration of postoperative analgesia of 5.3 (±1.8) hours. Because the morphine group required rescue at 13.3 hours on average, the apparent duration of analgesia with topical morphine was approximately 8 hours (i.e., 13.3 hours minus 5.3 hours).

The reported duration of analgesia induced by epidural morphine in dogs and cats ranges from 8 to 20 hours, depending on the analgesic model and pain assessment method used. In a tail clamp pain model in which pain was induced with a hemostatic clamp in dogs, a single dose of epidural morphine (0.1 mg/kg [0.045 mg/lb]) induced analgesia lasting 8 hours. Data are controversial when evaluating postoperative analgesia induced by preemptive epidural morphine in actual surgical cases. In one clinical study with a relatively large number of dogs (n = 24) undergoing orthopedic surgery, Kona-Boun and coworkers found that epidural morphine (0.2 mg/kg; n = 12) induced no significant improvement in postoperative pain scores compared with epidural saline (n = 12). Pacharinsak and associates reported that epidural administration of morphine (0.1 mg/kg) provided up to 12 hours of analgesia in dogs undergoing surgery to repair a ruptured cranial cruciate ligament. In our study, the analgesic effect of morphine applied topically next to the spinal cord was clearly demonstrated, with a duration of analgesia of approximately 8 hours—significantly longer than in the saline control group of dogs in this study.

Traditional epidural morphine administration is associated with systemic side effects. In a retrospective study, 242 dogs and 23 cats undergoing surgery received epidural morphine with or without bupivacaine; 7 dogs and 2 cats experienced urine retention, and 2 dogs developed pruritus. In another study, 6 dogs vomited when a second dose of epidural morphine was given the day after surgery and 8 of 72 dogs had delayed hair growth. Diaz and coworkers have since shown that delayed hair growth from 8 to 20 hours, depending on the analgesic model and pain assessment method used. In a tail clamp pain model in which pain was induced with a hemostatic clamp in dogs, a single dose of epidural morphine (0.1 mg/kg [0.045 mg/lb]) induced analgesia lasting 8 hours. Data are controversial when evaluating postoperative analgesia induced by preemptive epidural morphine in actual surgical cases. In one clinical study with a relatively large number of dogs (n = 24) undergoing orthopedic surgery, Kona-Boun and coworkers found that epidural morphine (0.2 mg/kg; n = 12) induced no significant improvement in postoperative pain scores compared with epidural saline (n = 12). Pacharinsak and associates reported that epidural administration of morphine (0.1 mg/kg) provided up to 12 hours of analgesia in dogs undergoing surgery to repair a ruptured cranial cruciate ligament. In our study, the analgesic effect of morphine applied in the lumbosacral region is due to the area clipped and likely not to the epidural procedure or morphine administration itself. An additional study reported that dogs receiving a lidocaine–bupivacaine combination with morphine developed bradycardia and hypotension soon after administration. In the current study, no cardiorespiratory depression, vomiting, pruritus, or urine retention was observed; further, heart and respiratory rates of treated dogs were similar to those of control dogs and were within normal ranges, indicating that topical application of morphine as described in this study was a relatively safe mode of administration.

In a human study, patients undergoing lumbar laminectomy were treated with topical application of microfibrillar collagen mixed with steroid hormone and preservative-free morphine and then infiltrated with 0.25% bupivacaine SC at wound closure. It was found that of 80 patients, 1 experienced clonic convolution...
and 4 developed deep wound infections.\textsuperscript{14} These side effects were not observed in our study. The differences observed could be related to the materials used during surgery as well as species variations.

The dosage of morphine used (0.1 mg/kg) in this study was extrapolated from a previous pilot study\textsuperscript{26} and is the most commonly used morphine dosage for epidural administration. It is unknown whether higher or lower doses of morphine would provide a similar degree and duration of analgesia when applied in this fashion. The fate of topically applied morphine is likely to follow that of epidural administration; that is, it diffuses across the dura mater and enters the subarachnoid space where the CSF is. Because of its low lipid solubility, morphine is capable of staying within the CSF longer than other opioids.\textsuperscript{5} This longer duration allows morphine to penetrate the spinal cord and act on the dorsal horn cells as well as supraspinal structures to modulate pain induced by the surgery. Further studies are needed to evaluate the dose effects on the duration of analgesia and side effects associated with topical morphine.

One of the limitations to this study is the small sample size. Animals in the saline control group had longer durations of clinical signs before surgery, and more dogs in this group required a myelogram for lesions to be located. Whether these two findings are associated with an increased severity of postoperative pain or could have shortened the duration of analgesia is unknown. A larger study with more animals in each group is required to confirm the efficacy of epidural morphine applied in this manner.

More study is needed to determine whether the use of the absorbable gelatin sponge contributes to an increased number of wound infections or to peridural fibrosis at the laminectomy site. An interesting future study could evaluate the release kinetics of the morphine from various vehicle substrates.

**CONCLUSION**

The results of this study indicate that topically applied epidural morphine given in the context of our anesthetic protocol was effective in providing postoperative pain management in dogs that underwent hemilaminectomy procedures to remove extradural compressions caused by Hansen type I disk extrusion. Topically administered preservative-free morphine applied via an absorbable gelatin sponge placed peridurally on the spinal cord at the time of surgery was effective in relieving pain in dogs undergoing hemilaminectomy.

**REFERENCES**


