Postoperative comparison of four perioperative analgesia protocols in dogs undergoing stifle joint surgery

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Objective—To compare 4 analgesic protocols in dogs undergoing stifle joint surgery.

Design—Randomized, blinded, prospective clinical trial.

Animals—48 client-owned dogs that underwent stifle joint surgery.

Procedures—Dogs undergoing tibial plateau leveling osteotomy were randomly assigned to receive a constant rate infusion of a combination of morphine, lidocaine, and ketamine; a lumbosacral epidural with morphine and ropivacaine; both treatments (ie, constant rate infusion and lumbosacral epidural); or only IM premedication with morphine. Indices of cardiorespiratory function and isoflurane requirement were recorded at 5-minute intervals during anesthesia. A validated sedation scoring system and the modified Glasgow composite measure pain score were used to assess comfort and sedation after surgery and anesthesia once the swallowing reflex returned and a body temperature of ≥36.7°C (98.1°F) was attained. Pain and sedation scores were acquired at 60-minute intervals for 4 hours, then at 4-hour intervals for 24 hours. Dogs with a postoperative pain score >5 of 24 were given morphine as rescue analgesia.

Results—No differences in heart rate, respiratory rate, systolic arterial blood pressure, end-tidal PCO₂, end-tidal isoflurane concentration, and vaporizer setting were detected among groups. No differences in pain score, sedation score, rescue analgesia requirement, or time to first rescue analgesia after surgery were detected.

Conclusions and Clinical Relevance—Pain scores were similar among groups, and all 4 groups had similar rescue analgesia requirements and similar times to first administration of rescue analgesia. All 4 analgesic protocols provided acceptable analgesia for 24 hours after stifle joint surgery.

Stifle joint surgery in dogs is associated with considerable postoperative pain.1–3 Opioids, N-methyl-D-aspartate receptor antagonists, local anesthetics, and NSAIDs are classes of analgesic drugs that have been administered to dogs both systemically and as part of a regional anesthetic technique (epidural) to provide relief from pain.4 Multimodal analgesia, the concurrent administration of multiple analgesic drugs and analgesic techniques, is a method of providing postoperative pain relief. Multimodal analgesia is purported to provide superior pain relief because the combination of drugs that act via different pathways has the potential to enhance efficacy.4,5 Morphine, an opioid analgesic, is used by a variety of routes and methods to produce analgesia.5–8 Morphine infusion alone and in combination with lidocaine and ketamine reduces the inhalation anesthesia requirement in dogs.7,8

The transfer of such studies to clinical medicine is difficult because the evaluation of the severity of pain in dogs is complex.9–20 The MGCMPS is a validated pain scoring system that uses multiple indices associated with orthopedic pain, including the patient’s overall appearance, observation of gait, response to pressure on the surgical site, and overall demeanor of the patient.12,13 Interpretation of the MGCMPS is made more difficult because sedation can alter the perception of the dog’s pain.

To our knowledge, no clinical study has systematically compared the postoperative sedation and analgesia associated with morphine administration alone with...
that of morphine administered epidurally along with a local anesthetic and morphine combined with lidocaine and ketamine as a CRI. The purpose of the study reported here was to determine whether the multimodal analgesic technique (ie, CRI of MLK and LE with MR) provides superior postoperative analgesia to that of IM administration of morphine alone (as a premedication), CRI of MLK alone, or LE with MR alone.

**Materials and Methods**

**Animals**—The Ohio State University Clinical Research Advisory Committee approved the study protocol. Client consent for enrollment in the study was obtained prior to surgery. Forty-eight adult client-owned dogs scheduled to undergo a TPLO of either stifle joint for a cranial cruciate ligament rupture were enrolled. Dogs were considered healthy on the basis of findings on physical examination, hematologic evaluation, serum biochemical analysis, and urinalysis. For sedation within 24 hours prior to surgery, the type and dose of drugs were recorded.

**Anesthetic and surgical protocols**—A physical examination was performed the day of the surgery. Rectal temperature, pulse, respiratory rate, body weight, mucous membrane color, hydration status, and American Society of Anesthesiologists preoperative status were determined and recorded on the anesthetic record. Concurrent medications, including NSAIDs, were also recorded.

Food, but not water, was withheld for ≥ 12 hours prior to anesthesia. Dogs were given acepromazine (0.02 to 0.1 mg/kg [0.009 to 0.045 mg/lb], IM; maximum dose, 3 mg) and morphine (0.4 mg/kg [0.18 mg/lb], IM) 20 minutes prior to IV catheter insertion. The dose of acepromazine was left to the discretion of the attending anesthesiologist and was based on the age of the dog and its temperament. An 18- or 20-gauge catheter was inserted into a cephalic vein for drug and crystalloid fluid administration. Anesthesia was induced with propofol (3 to 5 mg/kg [1.36 to 2.27 mg/lb], IV) given to effect, and the total dose was recorded. Dogs were orotracheally intubated and maintained with isoflurane in oxygen by use of an out-of-circuit precision vaporizer and a semiclosed circle anesthetic system. Initial vaporizer settings were adjusted according to clinical interpretation of anesthetic depth. Lactated Ringer’s solution (5 mL/kg/h, IV) was administered from the time of catheter insertion until closure of the skin after surgery. The CRI of MLK was administered after tracheal intubation until the end of surgical time. A Doppler probe was placed over a peripheral artery for pulse rate detection and an estimation of systolic arterial blood pressure with a sphygmomanometer and an appropriately sized cuff on the limb proximal to the Doppler probe. The cuff size was determined by laying an appropriately sized cuff on the limb proximal to the long axis of the cuff along the thoracic antebrachium and estimating the cuff width against the circumference of the limb. Cuff width was chosen to be approximately 40% of the underlying limb circumference. Heart rate, respiratory rate, and Doppler pressure were recorded. When transferred to the surgical suite, an oscillometric blood pressure monitor was attached to the previously placed cuff for measurement of systolic, diastolic, and mean arterial blood pressure. End-tidal PCO$_2$ (mm Hg) and end-tidal isoflurane concentration (vol%) were obtained from the multigas gas analyzer display. A lead II ECG was used to monitor heart rhythm. Body temperature was measured with an oroesophageal thermistor probe. Dogs were mechanically ventilated at a rate of 6 to 8 breaths/min and tidal volume of 10 to 15 mL/kg (4.5 to 6.8 mL/lb) to maintain end-tidal PCO$_2$ between 35 and 45 mm Hg. Mechanical ventilation was initiated when the dogs were transferred to the surgical suite and was discontinued prior to transfer to the radiology suite for postoperative radiography.

Data were recorded every 5 minutes from anesthetic induction through termination of surgery. The duration of total anesthesia, total surgical time, and time that the endotracheal tube was removed were recorded.

If a dog reacted to surgical stimulation (marked and sudden increase in heart rate, MAP, or both movement) and anesthesia could not be maintained with increasing isoflurane concentrations, hydromorphone (0.02 mg/kg [0.009 mg/lb], IV) was given and the dog was removed from the study.

If dysphoria occurred during recovery, acepromazine (0.02 to 0.05 mg/kg [0.009 to 0.023 mg/lb]) was administered IV. Morphine (0.4 mg/kg, IM) was administered as a rescue anesthetic to all patients with a postoperative pain score > 3 of 24. Patients were allowed to have NSAIDs at any time during the study; the type of NSAID, dosage, and times administered were recorded. The same surgeon (JD) performed all surgeries. Anarthroscopy was performed, and a TPLO was used to stabilize the stifle joint.

**Study design**—A blinded, randomized parallel design was used. Dogs were randomly assigned to receive CRI of a combination of morphine (0.24 mg/kg/h [0.11 mg/lb/h]), lidocaine (3 mg/kg/h), and ketamine (0.6 mg/kg/h [0.27 mg/lb/h]); morphine (0.2 mg/kg [0.09 mg/lb]) and 1% ropivacaine (0.2 mg/kg) epidurally (total volume delivered, 1 mL/4.5 kg of body weight [1 mL/9.9 lb] to a maximum of 10 mL); or both (CRI of MLK and LE with MR) or received no additional analgesia other than IM premedication with morphine (control). The CRI of MLK was begun after tracheal intubation and terminated at the end of surgical time.

Epidural administration of MR was performed by a veterinarian or anesthesia technician immediately before the dogs were transferred to the surgical suite. Epidural needle placement at the L7-S1 space was ensured by palpation of appropriate landmarks, followed by a loss of resistance technique. For dogs not receiving epidural anesthesia, hair was clipped over the epidural site and the site was covered with a bandage in the immediate postoperative period to prevent bias during pain scoring. Personnel collecting data were not allowed contact with the patient until time 0 (first postoperative pain score assessment) and also had no access to anesthetic records.

Assessments were performed by 1 of 2 trained evaluators. Pain and sedation assessments began after surgery when the patient had a body temperature of ≥ 36.7°C (98.1°F) and the swallowing reflex had returned.
(time 0). Pain and sedation scores were recorded at time 0, hourly for the first 4 hours, and then every 4 hours until 24 hours after surgery. An MGCMPS12,15 was used to assess pain scores. Variables assessed included vocalization, attention to wound area, mobility, response to touch, demeanor, and posture. Dogs with pain scores > 5 (out of a possible total of 24) received morphine as rescue analgesia (0.4 mg/kg, IM).

A validated sedation scoring system26 was used to assess sedation in all of the patients. Variables assessed included vocalization, posture, appearance, interactive behaviors, response to restraint (restraint was defined as the position typical for cephalic catheterization: arm around neck with forelimb outstretched), and noise response (4 loud hand claps within 12 inches of the patient’s head). The sedation score results were recorded but did not affect whether the patient received rescue analgesia.

Statistical analysis—Data were tested graphically for normality (by visual inspection of histograms and residual plots) and formally (by the Shapiro-Wilk test). If the data were not normally distributed, the data were transformed to normalcy or a nonparametric analysis (Kruskal-Wallace test) was applied. The median and range were reported for data that were not normally distributed, and the mean ± SD was reported for data that were normally distributed. Differences among pain scores were tested by means of a nested-factorial ANOVA, only if successfully transformed to normalcy) design (4 treatment groups, fixed variable; 12 patients, random variable nested within each group; 10 measurements from time 0, fixed variable [crossed with group and applied to each patient]). Two-sided tests were used to allow the possibility of detecting unexpected relationships, and α was set at 0.05. To determine which protocols were different, appropriate multiple comparisons procedures (Newman-Keuls procedure if the data were normally distributed) were used for all significant differences between > 2 groups (or patients or times).

Results

Seventeen breeds were represented in this study, including 14 mixed-breed dogs, 6 Labrador Retrievers, 5 Golden Retrievers, 4 German Shepherd Dogs, 3 Great Pyrenees, 3 Newfoundlands, 2 American Bulldogs, 2 Rottweilers, and 1 dog each for 9 other breeds (American Cocker Spaniel, Bearded Collie, Catahoula Leopard Hound, Chow Chow, Dalmatian, Doberman Pinscher, German Shorthair Pointer, Great Dane, and Siberian Husky). Treatment groups did not differ significantly with regard to American Society of Anesthesiologists status, body weight, sex distribution, or age.

Dogs received 1 of 5 NSAIDs (carprofen, deracoxib, firocoxib, meloxicam, and piroxicam). On the day prior to surgery, NSAIDs were administered per usual instructions. The morning of surgery, NSAIDs were withheld. After surgery, NSAIDs were administered to all patients. Patients were receiving an NSAID for a mean duration of > 10 days prior to entry into the study. The distribution of NSAID use was not different among groups. Carprofen was the most commonly used NSAID. The dose of acetylsalicycine used for preoperative sedation was not different among groups (0.05 ± 0.02 mg/kg [0.023 ± 0.009 mg/lb] to 0.06 ± 0.02 mg/kg [0.027 ± 0.009 mg/lb]). The dose of propofol was 5 mg/kg (1.82 mg/lb) for all groups. Mean ± SD heart rate, respiratory rate, systolic arterial blood pressure, end-tidal Pco₂, end-tidal isoflurane concentration, vaporizer percentage at anesthetic induction, and vaporizer percentage during the surgical period were not different among groups.

Duration of anesthesia, duration of surgery, and time to extubation were not different among groups. Duration of anesthesia among groups ranged from 135 ± 18 minutes to 145 ± 28 minutes. Duration of surgery among groups ranged from 58 ± 7 minutes to 72 ± 25 minutes. Time to extubation among groups ranged from 16 ± 16 minutes to 43 ± 31 minutes. Some dogs in each group received rescue analgesia over the 24-hour postoperative period (Figure 1). A Kaplan-Meier time to rescue analgesia curve denoted the percentage of dogs without any rescue analgesia remaining over time in each treatment group. Numbers of dogs requiring rescue analgesia, time to rescue analgesia administration, mean dose of rescue analgesia, and number of rescue analgesia doses were not different among groups (Table 1).

During the data collection phase, 53 dogs were originally enrolled. Five dogs were removed from the study prior to pain scoring. One dog was removed because of a skin infection over the surgical site. Three dogs were removed during surgery because of complications related to the surgical procedure itself, which did not impact the anesthetic episode. Lastly, 1 dog was removed after surgery because additional drugs were inadvertently administered. Data from removed dogs were not included in the analysis. Data analysis was performed on the 48 dogs enrolled in the study.

The maximum possible sedation score was 14. Mean sedation scores ranged from 5.2 to 7.8 and were not different among groups. Sedation decreased over time and at the same rate. The maximum pain score possible was 24. Mean pain scores over time ranged from 2.6 to 2.8, with no difference among groups for the mean pain score (Table 2). Median and mean pain scores among groups were not different over time. Pain scores among groups were not different over time. Pain scores among groups were not different over time.
Discussion

Each of the 4 analgesic protocols provided adequate pain relief in this group of dogs after stifle joint surgery on the basis of the number of dogs requiring rescue analgesia. The quality of pain relief produced was equivalent in the 4 groups on the basis of the MGCMPS, and the degree of sedation was similar. In this population of dogs undergoing stifle joint surgery, the use of multimodal analgesia (opioid-NSAID combination plus CRI of MLK, LE with MR, or both CRI and LE protocols) did not significantly improve comfort, compared with an opioid-NSAID combination alone. There was no difference among groups in the number of dogs requiring rescue analgesia, the time until first rescue analgesia was administered, mean cumulative dose of rescue analgesia, or mean number of rescue analgesia doses administered. Some dogs in each group required rescue analgesia at some point in the 24-hour postoperative period.

When comparing mean pain scores at each time point, we included all dogs regardless of whether they received rescue analgesia. Several dogs in each group received rescue analgesia within 1 to 2 hours after surgery, potentially minimizing pain scoring differences among groups. The pain score SDs were large in each group at each time point, and this probably contributed to finding no difference among groups. Data were reexamined after removing all dogs that received rescue analgesia, and no difference in mean pain scores among the groups were found, although the SDs appeared smaller. No trend was found in any group in rescue analgesia requirements for either the number of doses or the time to first rescue analgesia administration. In a study that examined the effects of perioperative analgesic protocols (epidural injection, intra-articular injection, and IV injection) for management of postoperative pain in dogs after TPLO, Hoelzler et al24 found no differences in measured indices of postoperative pain among groups (epidural, intra-articular, and IV) but the epidural and intra-articular groups had longer times to the administration of the first rescue analgesia, compared with the control group. Differences in our study versus that study24 may be due to different epidural drug combinations, drug concentrations, or drug formulations. Hoelzler et al24 used a morphine dose of 0.1 mg/kg, which was less than our dose of 0.2 mg/kg. The dose of local anesthetic used in the study by Hoelzler et al24 was greater than the local epidural anesthetic used in the present study. This lower dose of morphine and higher concentration of local anesthetic could have accounted for some of the differences in outcomes between the 2 studies. Additionally, Hoelzler et al24 used 2 pain scoring methods, neither of which has been validated in assessing acute orthopedic pain.

Our pain score results are contrary to those from other studies21,27,28 comparing analgesia protocols in orthopedic procedures during the 24-hour postoperative period. Hendrix et al27 compared the analgesic effects of epidurally administered morphine, bupivacaine hydrochloride, and both in combination versus sterile saline (0.9% NaCl) solution in dogs undergoing various hind limb orthopedic surgeries. All groups received an opioid as a premedication, and the epidural administration was performed after surgery. That study27 found that pain scores are lower in dogs receiving the combination, that the time to administration of rescue analgesia is longer for dogs in the combination group, and that the number of rescue analgesia boluses administered is lower in the combination groups than in dogs receiving saline solution. Those investigators used a greater local anesthetic concentration than that used in the present study, and their epidural combinations may have provided better analgesia and resulted in a difference in pain scores among groups. The concentration of local anesthetic in the epidural used in the present study was

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Table 1—Summary of rescue analgesia data for 48 client-owned dogs that underwent a unilateral TPLO and received a CRI of MLK (n = 12), an LE with MR (12), or both CRI and LE protocols (12) or that received no additional analgesia other than morphine premedication IM (control; 12).

<table>
<thead>
<tr>
<th>Variable</th>
<th>CRI of MLK (n = 12)</th>
<th>LE with MR (n = 12)</th>
<th>Both CRI and LE protocols (n = 12)</th>
<th>Morphine only (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of dogs requiring rescue analgesia</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Mean time to rescue analgesia administration (h)</td>
<td>5.6±7</td>
<td>7</td>
<td>4.6</td>
<td>13.7</td>
</tr>
<tr>
<td>Mean dose of morphine as rescue analgesia (mg/kg)</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Mean No. of rescue analgesia doses</td>
<td>2.8</td>
<td>2.3</td>
<td>1.6</td>
<td>3</td>
</tr>
<tr>
<td>Time of earliest rescue analgesia administration (h)</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

An MGCMPS and a sedation score were recorded at time 0, hourly for the first 4 hours, and then every 4 hours until 24 hours after surgery. A maximum score of 24 could be achieved. Dogs with pain scores > 7 received morphine as rescue analgesia (0.4 mg/kg, IM).

Table 2—Mean ± SD pain scores of the same dogs as in Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total pain score</th>
</tr>
</thead>
<tbody>
<tr>
<td>All dogs (n = 48)</td>
<td>2.9 ± 1.9</td>
</tr>
<tr>
<td>CRI of MLK (n = 12)</td>
<td>2.8 ± 2.0</td>
</tr>
<tr>
<td>LE with MR (n = 12)</td>
<td>2.8 ± 1.9</td>
</tr>
<tr>
<td>Both CRI and LE protocols (n = 12)</td>
<td>2.8 ± 1.6</td>
</tr>
<tr>
<td>Morphine only (n = 12)</td>
<td>2.8 ± 1.6</td>
</tr>
<tr>
<td>Dogs not receiving rescue analgesia (n = 32)</td>
<td>2.0 ± 1.0</td>
</tr>
<tr>
<td>CRI of MLK (n = 8)</td>
<td>2.0 ± 0.9</td>
</tr>
<tr>
<td>LE with MR (n = 8)</td>
<td>2.2 ± 1.0</td>
</tr>
<tr>
<td>Both CRI and LE protocols (n = 7)</td>
<td>2.0 ± 1.1</td>
</tr>
<tr>
<td>Morphine only (n = 8)</td>
<td>2.1 ± 1.0</td>
</tr>
</tbody>
</table>

Pain scores were plotted against a maximum score; no group had a mean pain score > 7.
chose to avoid paralysis, which could confound pain scoring results but also increase the duration of effect of the epidural. Hendrix et al25 also used a smaller morphine dose of 0.1 mg/kg for epidural administration, which was lower than our dose of 0.2 mg/kg. Differences from our study in opioid dosages and the associated durations of analgesia could have accounted for the longer duration until the need for rescue analgesia in that study.27 Lastly, the surgical procedures were not standardized in that study27; various orthopedic procedures involving the hind limbs or pelvis were included.

All dogs in the present study received NSAIDs prior to admission for surgery, and all dogs were administered an NSAID after extubation or at 8:00 PM following their surgery. If they were receiving carprofen, they received a subcutaneous injection at extubation. Carprofen was the most commonly administered NSAID. The other NSAIDs administered during the postoperative period included meloxicam, piroxicam, deracoxib, and firocoxib. The NSAID-associated anti-inflammatory and analgesia properties could have contributed to masking differences in analgesia among groups in our study. The different types of NSAIDs and associated doses specific to each NSAID could have affected the results of this study. All dogs in this study received NSAIDs for > 7 days prior to surgery. Several studies2,20–37 have shown the analgesic efficacy of NSAIDs used in conjunction with opioids. Because NSAIDs take ≥ 7 days to wash out24 and because our subjects were client-owned dogs, ethically, we elected to continue their NSAIDs before and after surgery. The additional NSAIDs administered to all patients in the present study could have further supplemented analgesia, resulting in similar pain scores among groups.

Having multiple people perform epidural drug administration may have influenced our results, given that we did not confirm epidural needle placement with radiography. Everyone was similarly trained in the loss of resistance technique and used the same anatomic landmarks to identify the location of needle entry. The failure rate should have been similar among individuals, and no single individual performed the epidurals exclusively in one group or the other. Factors such as volume of injectate, orientation of the needle bevel, type of needle, and variations in individual anatomy can influence the success and extent of drug distribution.25 Other than variations in individual anatomy, we controlled most of the other variables to the extent permitted by the study design.

All 4 analgesic protocols we used have been shown to reduce intraoperative isoflurane requirement.2 It is for this reason that we did not see a difference among groups in intraoperative cardiovascular data and anesthetic depth. This project was not designed to be a minimum alveolar concentration study comparing the intraoperative inhalation anesthetic–sparing capacity of each group. Even so, the lack of minimum alveolar concentration–sparing effect shown intraoperatively should not have impacted the pain scoring in the postoperative period.26

It is possible that differences existed in the quality of analgesia provided by each of these protocols but that we were unable to detect a difference among groups. Multiple confounding factors affect the diagnostic validity of pain scoring.9,12 These factors include psychological and behavioral status as well as administration of anxiolytics, narcotics, and other agents. Methods of scoring pain in animals rely on the observer’s interpretation of animal behavior.9–12 The MGCMPS has been validated for use in dogs with orthopedic pain. Smaller interobserver variation has been shown, and results are less influenced by sedation than other scoring systems.12,13 Large SDs were seen within our groups, and consequently, this may have contributed to the lack of any differences. The addition of an alternate pain scoring system may have been more sensitive in detecting differences in pain scores among groups.11,17,18 Therefore, the administration of morphine as a postoperative rescue analgesic in the present study might have influenced subsequent MGCMPS scores.

Sedation can affect pain scoring even though the MGCMPS was shown to be less affected by sedation than other scoring systems.10,12,39,40 It is possible that all protocols used in the present study provided similar pain control because all groups had similar low mean pain scores during the 24-hour postoperative period. These 4 protocols are all commonly used for pain control for various orthopedic procedures. Perhaps if we had monitored these dogs for a longer period after surgery, we would have found significant differences among groups in long-term analgesic requirements. For example, epidurally administered morphine has been shown to provide analgesia for up to 24 hours.6,41 However, our study was designed to compare analgesia in the 24-hour postoperative period. All groups benefited from regular evaluation of pain and assessment of analgesia requirements throughout the 24-hour period. From our data, we can conclude that all 4 techniques provided similar, effective analgesia and sedation for 24 hours after surgery.

References


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