Comparison of ketoprofen and carprofen administered prior to orthopedic surgery for control of postoperative pain in dogs

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Objective—To compare analgesic and adverse effects of ketoprofen and carprofen when used to control pain associated with elective orthopedic surgeries in dogs.

Design—Prospective randomized clinical trial.

Animals—93 client-owned dogs: 46 undergoing reconstruction of the cranial cruciate ligament, 47 undergoing femoral head and neck excision, and 15 control dogs anesthetized for radiographic procedures.

Procedure—Dogs undergoing surgery were randomly given ketoprofen, carprofen, or saline (0.9% NaCl) solution, SC, prior to surgery. Pain score and serum cortisol concentration were recorded for 12 hours after surgery for all dogs. When pain score was ≥ 7, oxymorphone was administered IM. Bleeding time was measured prior to and during surgery.

Results—The proportion of dogs that required oxymorphone was significantly higher for the carprofen and placebo groups than for the ketoprofen group. Pain score for the placebo group was significantly higher than for the ketoprofen and carprofen groups, 2, 8, and 9 hours after surgery. Cortisol concentration was significantly higher for the placebo group than for the carprofen group at 4 and 6 hours after surgery. Significant differences were not detected between ketoprofen and carprofen groups with respect to pain score and cortisol concentration. Bleeding time was significantly longer for the ketoprofen group than for the other groups during surgery. One dog treated with ketoprofen developed a hematoma at the surgical site.

Conclusions and Clinical Relevance—Ketoprofen and carprofen given prior to surgery were effective for postoperative pain relief in dogs. However, ketoprofen should not be used when noncompressible bleeding may be a problem. (J Am Vet Med Assoc 1999;215:1105–1110)

Opioids have long been the drugs of choice for control of postoperative pain. However, their potential adverse effects (hypoventilation and bradycardia) are not negligible.1 During the past few years, development of new veterinary labeled nonsteroidal anti-inflammatory drugs (NSAID) has promoted use of this class of analgesic drug in the perioperative period.2 Ketoprofen and carprofen are new potent NSAID with well established analgesic properties in dogs.3 Both are propionic acid derivatives. Ketoprofen is a potent inhibitor of cyclooxygenase, with some in vitro inhibitory effect on lipooxygenase and on synthesis of bradykinin.4 Therefore, it inhibits synthesis and release of prostaglandins, and to some extent synthesis of leukotrienes, leading to a peripheral analgesic effect common to most NSAID.5 Ketoprofen also provides analgesic effects at the central level.6,7 Carprofen is a weak inhibitor of cyclooxygenase, but this alone does not explain its analgesic properties. A central action has been hypothesized but has not been clearly demonstrated.7,10,11 Adverse effects common to NSAID (eg, gastric and duodenal ulcers, renal failure, and hemorrhage) are caused by inhibition of prostaglandin synthesis. However, ketoprofen and carprofen seem to be well tolerated by dogs when used at the recommended dosage.7,12,13

A major component of postoperative pain is induced by peripheral and central sensitization of structures involved in nociception. This leads to an exaggerated responsiveness to noxious stimuli (hyperalgesia), a spread of hypersensitivity to noninjured tissue (secondary hyperalgesia), and a reduction in intensity of stimuli necessary to initiate pain (allodynia). This can be minimized by use of analgesic drugs prior to painful stimulation, such as surgery. Benefits of preemptive analgesia have been demonstrated for opioids14 and carprofen.15,16 This should also apply to other NSAID, although to our knowledge, this has not yet been confirmed.17

The purpose of the study reported here was to compare the efficacy of analgesia provided by ketoprofen and carprofen and the nature and importance of their adverse effects when administered prior to orthopedic surgery in dogs.

Materials and Methods

Preoperative assessment—Ninety-three dogs referred for orthopedic surgery were used. All dogs had severe hind limb lameness. Physical and radiographic examinations confirmed diagnosis of femoral neck fracture, acetabular fracture, hip dysplasia, or cranial cruciate ligament rupture. All owners elected surgical treatment. Forty-seven dogs underwent femoral head and neck excision, and 46 underwent reconstruction of the cranial cruciate ligament. Fifty females and 43 males between 4.5 and 121 months old and weighing
4 to 55 kg were included. Owners of all dogs gave informed consent. Exclusion criteria were pregnancy, evidence of renal or hepatic dysfunction, gastrointestinal disease, and coagulation disorders.

Fifteen dogs of similar age and breed were used as controls for postoperative pain assessment. They underwent the same postoperative evaluations, but were anesthetized only for radiographic procedures. Protocol of this study was approved by the Animal Care Committee of our institution and was in accordance with the Guidelines of the Canadian Council for Animal Care.

Medical history was recorded for each dog. General behavior and compliance to restraint and injection of medication were assessed by use of a reported scoring system (Appendix 1). Blood samples were collected the day before surgery from the jugular vein to determine baseline value of serum cortisol concentration. Bleeding time was also measured at this time using a lancet at the internal aspect of the ear. Dogs with a bleeding time > 300 seconds were excluded.

Anesthesia and surgery—Dogs undergoing surgery were assigned by random draw to 1 of 3 treatment groups: ketoprofen (2 mg/kg [0.9 mg/lb], SC), carprofen (0.18 mg/kg [0.4 mg/lb], IM), and placebo (0.9% NaCl, SC). This was a blind study; treatment was administered at the same time as preanesthetic drugs and was not known at any time by the person administering the drug or assessing postoperative pain.

Dogs were premedicated with glycopyrrolate (0.01 mg/kg [0.0045 mg/lb], IM) and acepromazine (0.1 mg/kg [0.045 mg/lb], IM). Thirty minutes later, anesthesia was induced with thiopental sodium (10 mg/kg [4.55 mg/lb], IV) to allow for orotracheal intubation. Anesthesia was maintained with isoflurane in oxygen by use of a semiclosed rebreathing system. Oxygen flow rate was set between 20 and 30 ml/kg/min and isoflurane concentration was adjusted between 1.5 and 3 on the vaporizer to maintain an adequate plane of anesthesia. Lactated Ringer’s solution was administered IV during anesthesia at a rate of 10 ml/kg/h (4.55 mg/lb/h). Prophylaxis was ensured by IV administration of cefazolin sodium 30 minutes before surgery and every 2 hours thereafter until completion of surgery. Surgery was performed by 1 of 5 surgeons. Recovery of glutathione reflux was used as the criterion for extubation in all dogs. Duration of anesthesia and surgery was recorded.

Buccal mucosa bleeding time was measured 1 hour after administration of analgesic treatment and at completion of surgery. Surgeons were asked to subjectively assess surgical bleeding (0 = normal bleeding, 1 = slight increase in bleeding, 2 = obvious increase in bleeding). Control dogs were anesthetized using the same protocol as dogs requiring surgery. They did not receive analgesic treatment and did not undergo any surgical procedure.

Postoperative assessment—For 12 hours after surgery, heart rate, direct arterial blood pressure, pain score, and sedation score were recorded hourly. Measurement of systolic, diastolic, and mean arterial pressures were performed through a catheter placed in the dorsal pedal artery just after induction of anesthesia. Pain score was determined by the same observer in all dogs as described (Appendix 2). A dose of oxymetacaine (0.05 mg/kg [0.227 mg/lb]) was administered IV during surgery when analgesia was considered to be inadequate on the basis of persistence of tachycardia (heart rate > 140 bpm) or hypertension (mean arterial blood pressure > 130 mm Hg). After surgery, a dose of oxymetacaine was administered IM if the total pain score was ≥ 7. Total amount and time of administration of supplemental oxymetacaine doses were recorded. Use of 7 as a trigger score for interventional treatment was based on experience with this pain scoring system used for research and clinical purposes in our institution. Pain score could not be determined in a blinded manner for the dogs of the control group, since it was apparent that they did not undergo surgery.

Serum cortisol concentration was measured after completion of anesthesia and again at 2, 4, 6, and 12 hours. Samples were stored at −70°C and analyzed within 12 months of collection. Cortisol concentration was determined by use of solid phase radioimmunoassay. Adverse effects, such as gastrointestinal (vomiting, diarrhea) and blood coagulation disorders (excessive bleeding at surgical site), were recorded for 48 hours following surgery.

Statistical analysis—Data were expressed as mean ± SEM. Preoperative and intraoperative data were compared using an unpaired Student t-test and a χ² test for continuous and discrete variables, respectively. Data collected after administration of oxymetacaine (for supplemental analgesia) during or after surgery were excluded from statistical analysis. The proportion of dogs not requiring a supplemental dose of oxymetacaine was evaluated, using survival analysis. Actuarial estimates were calculated for the 3 treatment groups and the control group using the Kaplan-Meier technique and then compared with the log-rank test.

Postoperative pain score, arterial blood pressures, bleeding time, and serum cortisol concentration were analyzed using a repeated-measures ANOVA followed by a Student-Newman-Keuls pairwise comparison procedure to evaluate effects of time after surgery and analgesic treatment. A forward stepwise regression analysis was performed to identify factors that significantly influenced pain score and serum cortisol value after surgery. Relevant variables tested were breed, age, sex, and weight; preoperative behavior and compliance; duration of anesthesia and surgery; type of surgery; surgeon, analgesic treatment, and time after surgery. Values of P < 0.05 were considered significant.

Results

Significant differences among treatment groups were not detected in regard to age, breed, sex, weight, preoperative behavior, and compliance scores. Duration of anesthesia and surgery was similar among treatment groups (183 ± 5 minutes and 101 ± 4 minutes) but anesthesia was shorter for control dogs (38 ± 5 minutes). In multivariate analysis, time after surgery and analgesic treatment were the only independent determinants of postoperative pain score and serum cortisol concentration.

Control dogs had a pain score ≤ 6 and did not require supplemental treatment with oxymetacaine (Fig 1). Twenty-one of the 93 dogs that underwent orthopedic surgery (from all 3 treatment groups) received oxymetacaine because of signs of inadequate analgesia. The percentage of dogs that required oxymetacaine during or after surgery and were excluded from further analysis was 15% (5/34 dogs) for the ketoprofen group, 27% (8/30) for the carprofen group, and 28% (8/29) for the placebo group. This percentage was significantly higher for carprofen and placebo groups than for controls. There was not a significant difference between groups in regard to total amount of oxymetacaine administered (ketoprofen, 0.015 ± 0.007 mg/kg; carprofen, 0.02 ± 0.007 mg/kg; placebo, 0.02 ± 0.007 mg/kg; P = 0.73) and time to first administration (ketoprofen, 122 ± 79 minutes; carprofen, 82 ± 25 minutes; placebo, 164 ± 63 minutes; P = 0.55).

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The mean pain score for controls was significantly lower overall than for ketoprofen, carprofen, and placebo groups (Fig 2). Pain score for the placebo group was significantly higher than for the ketoprofen group at 2 hours after surgery, and for the carprofen group at 2, 8, and 9 hours after surgery ($P = 0.01$). A significant difference between ketoprofen and carprofen groups was not detected.

Baseline serum cortisol concentration did not differ significantly among the 3 treatment groups. After surgery, mean cortisol concentration for controls was significantly lower than for ketoprofen and placebo groups at all times, and than for carprofen group at 0, 2, and 8 hours after surgery (Fig 3). Mean cortisol concentration was significantly lower at 4 and 6 hours after surgery for the carprofen group than for the placebo group. A significant difference in mean cortisol concentration was not detected between the ketoprofen and carprofen groups.

Significant differences were not detected among groups in regard to systolic, diastolic, and mean arterial pressures after surgery ($P = 0.90$) or among groups in regard to bleeding time prior to medication. Mean bleeding time was significantly longer in the ketoprofen group than in placebo and carprofen groups at the beginning and end of surgery (Fig 4). However, intraoperative bleeding score estimated by the surgeons was not significantly different among groups. There was not a correlation between mucosal bleeding time and intraoperative bleeding score.
Increased intraoperative bleeding, combined with prolonged bleeding time (375 seconds and 496 seconds at beginning and completion of surgery, respectively), and persistent bleeding from the incision, was observed in 1 dog that received ketoprofen. Severe dissection at the surgical site (stifle) caused by a hematoma was detected 1 day after surgery. At this time, mucosal bleeding time (90 seconds) had returned to normal. Furthermore, prothrombin time (6.6 seconds), activated partial thromboplastin time (17.9 seconds), and factor VIII related antigen (von Willebrand factor; 87%) were within reference range. A compressive bandage was applied and the hematoma resolved.

**Discussion**

Reliability of pain scoring in animals depends highly on criteria selected in scoring and the importance attributed to these criteria. A recent study demonstrated that significant variability exists among observers for estimation of pain score, using a simple descriptive scale, numerical rating scale, or visual analogue scale. Serum cortisol concentration is recognized as one of the most objective criteria for pain assessment in dogs and cats. This variable is useful for research studies comparing the efficacy of analgesic drugs. However, determination of serum cortisol concentration is not useful in clinical management of acute postoperative pain, because results cannot be rapidly obtained. Therefore, other tools, such as pain scoring systems, must be relied on to assess the need for pain relief.

Inclusion of a placebo group is important in studies comparing various analgesic treatments. Validation of the pain scoring system is appropriate only when results of dogs not having signs of pain (control dogs) are compared with dogs not receiving analgesics (placebo dogs). Efficacy of analgesic treatment cannot be proven until a placebo controlled randomized clinical trial is performed. From an ethical standpoint, it is possible to design a humane study that includes an untreated control group but incorporates interventional treatment if signs of pain increase above a predefined threshold.

Because there is not a specific physiologic marker of pain, multiple criteria must be looked at to provide sufficient information in assessing pain. The pain scoring system used in the study reported here was based on the combination of 5 physiologic or behavioral variables, to improve sensitivity and specificity of total pain score. A pain score ≤ 6 may indicate mild pain, postoperative excitement, or stress (fear, anxiety). Threshold score was set at 7, so that animals experiencing moderate or severe pain would receive oxymorphone. This pain scoring system had been indirectly validated in a study where a correlation existed between pain score and cortisol concentration.

Validation of pain assessment requires inclusion of animals which received the anesthetic but did not undergo any surgery to determine effects of anesthesia in the absence of painful procedure. One of the control dogs included in this study had a pain score of 6 at 7 hours after surgery, but none experienced a pain score higher than the predetermined level of 7 used for interventional treatment. Mean pain score for the control group was significantly lower than for the placebo group during the 12 hours after surgery, except at 4 and 7 hours postoperatively. This absence of statistical difference could be attributable to an underestimation of the pain score of placebo dogs or to an increase in the pain score of control dogs because of excitement after anesthetic recovery. In this context, it should be considered that the duration of anesthesia was shorter in the control group than in the other groups. This could have contributed to faster recovery and earlier excitement in this group. Nonetheless, the mean pain score for controls was clearly lower than that of the placebo group during the postoperative period, and significant differences were detected in 10 of 12 evaluation times.

It was surprising that 72% of the 29 placebo dogs included in this study did not require analgesic treatment. The relatively low requirement for intervention in the placebo group seems to indicate that sensitivity of this interventional system still remains too low, although the threshold for interventional analgesic treatment had been set at 7 in this study instead of 9 in another one in which the same scoring system was used. However, decreasing the threshold to 5 or 6 would have led to a lack of specificity. Unfortunately, a highly sensitive and specific system for pain assessment in animals does not exist at this time.

Results of serum cortisol concentration are also consistent with those of pain score. Mean serum cortisol concentrations were similar in control and placebo groups before anesthesia. At the end of anesthesia and for 8 hours thereafter, mean cortisol concentration was markedly lower for the control group than for the placebo group. These results further support the reliability of the pain scoring system used in this study and of serum cortisol concentration to assess efficacy of various analgesic treatments after orthopedic surgeries in dogs.

Several recent studies demonstrate ketoprofen and carprofen are more effective than most opioids for relief of postoperative pain in dogs. Ketoprofen administered at the end of surgery was more efficacious than butorphanol and oxymorphone for pain relief in dogs following orthopedic surgery, and carprofen provided better postoperative analgesia than did papaveretum or meperidine hydrochloride.

Significant differences between ketoprofen and carprofen groups were not detected during the 12 hours after surgery, in regard to number of dogs that required oxymorphone, total amount of oxymorphone administered, pain score, or serum cortisol concentration. The proportion of dogs requiring oxymorphone was higher in the carprofen group (26.7%) than in the ketoprofen group (14.7%), but the mean pain score was lower in the carprofen group than in the ketoprofen group from 6 to 12 hours after surgery. On the basis of these results, carprofen and ketoprofen given prior to orthopedic
surgery provide similar levels and durations of postoperative analgesia.

Carprofen was associated with significantly lower serum cortisol concentration, compared with the placebo group, thus indicating a significant reduction in the stress response to surgery. This was not observed for ketoprofen. Because significant differences were not detected between carprofen and ketoprofen groups (compared with placebo group), it is inappropriate to conclude that carprofen is more effective than ketoprofen for pain relief following orthopedic surgery. Additional studies in other species and with other types of surgery could be useful to further compare analgesic effects of these drugs.

Only ketoprofen was associated with increased bleeding time. It is a more potent inhibitor of cyclooxygenase (COX) and thromboxane synthesis than carprofen and can cause an increased inhibition of platelet aggregation. However, it is uncertain whether an increase in mucosal bleeding time is associated with increased blood loss during or after surgery. In our study, there was no correlation between bleeding time and intraoperative bleeding score estimated by the surgeon. This result is in agreement with other studies that also failed to demonstrate any association between mucosal bleeding time and surgical blood loss. Bleeding time is a weak indicator of hemorrhage risk, and its use as routine preoperative test is now controversial in human medicine. Nonetheless, antithromboxane effects of ketoprofen and other potent inhibitors of COX 1 must be considered, and preoperative administration should not be undertaken in dogs with coagulation disorders.

Arterial blood pressure should be adequately monitored if any NSAID is administered prior to surgery, because inhibition of COX also interferes with renal perfusion and may lead to acute renal failure if hypotension is prolonged during anesthesia. Carprofen is approved for preoperative use and appears to be safer than ketoprofen because of its poor inhibition of COX and its COX 1:COX 2 ratio ≤ 1. Preoperative use of ketoprofen should be considered relative to overall status of the patient because of its strong inhibition of COX.

Ketoprofen and carprofen administered prior to surgery were effective in relieving postoperative signs of pain following elective orthopedic surgery in dogs. However, analgesia was not optimal, because both drugs failed to abolish the increase in pain score and cortisol concentration during and after surgery. It is recommended to combine these drugs with other analgesic treatments such as parenteral, transdermal, or epidural administration of opioids, or locoregional block. Multimodal and preemptive analgesic treatment is probably the best approach to optimize reduction of surgical pain and prevent postoperative stress response.

Appendix 1
Criteria used for scoring preoperative behavior and compliance in dogs

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavior</td>
<td></td>
</tr>
<tr>
<td>Anxious</td>
<td>1</td>
</tr>
<tr>
<td>Anxious, submissive behavior</td>
<td>2</td>
</tr>
<tr>
<td>Very anxious, tries to move away</td>
<td>3</td>
</tr>
<tr>
<td>Aggressive</td>
<td>4</td>
</tr>
<tr>
<td>Compliant with restraint and medication injection</td>
<td>5</td>
</tr>
<tr>
<td>No objection</td>
<td>0</td>
</tr>
<tr>
<td>Recovers injection, no complaint</td>
<td>1</td>
</tr>
<tr>
<td>Objects, but does not try to bite</td>
<td>2</td>
</tr>
<tr>
<td>Tries to bite, struggles violently</td>
<td>3</td>
</tr>
</tbody>
</table>

Appendix 2
Criteria used for scoring postoperative pain in dogs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>0 to 10% greater than preoperative value</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>11 to 30% greater than preoperative value</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>31 to 50% greater than preoperative value</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&gt; 50% greater than preoperative value</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory pattern</td>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Mild abdominal assistance</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Marked abdominal assistance</td>
<td>2</td>
</tr>
<tr>
<td>Vocalization</td>
<td>No crying</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Crying, responds to calm voice</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Crying, does not respond to calm voice</td>
<td>2</td>
</tr>
<tr>
<td>Agitation</td>
<td>Asleep or calm</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Mild agitation</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Moderate agitation</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Severe agitation</td>
<td>3</td>
</tr>
<tr>
<td>Response to manipulation</td>
<td>No response</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Minimal response, tries to move away</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Tense head toward site, slight vocalization</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Tense head with intention to bite, howls</td>
<td>3</td>
</tr>
</tbody>
</table>

References


