Use of low doses of ketamine administered by constant rate infusion as an adjunct for postoperative analgesia in dogs

Ann E. Wagner, DVM, MS, DACVP, DACVA; Judy A. Walton; Peter W. Hellyer, DVM, MS, DACVA; James S. Gaynor, DVM, MS, DACVA; Khursheed R. Mama, DVM, DACVA

Objective—To compare indicators of postoperative pain and behavior in dogs with and without a low-dose ketamine infusion added to usual perioperative management.

Design—Prospective, randomized, blinded clinical study.

Animals—27 dogs undergoing forelimb amputation.

Procedure—Dogs were anesthetized with glycopyrrolate, morphine, propofol, and isoflurane. Thirteen dogs were treated with ketamine IV, as follows: 0.5 mg/kg (0.23 mg/lb) as a bolus before surgery, 10 µg/kg/min (4.5 µg/lb/min) during surgery, and 2 µg/kg/min (0.9 µg/lb/min) for 18 hours after surgery. Fourteen dogs received the same volume of saline (0.9% NaCl) solution. All dogs received an infusion of fentanyl (1 to 5 µg/kg/h [0.45 to 2.27 µg/lb/h]) for the first 18 hours after surgery. Dogs were evaluated for signs of pain before surgery, at the time of extubation, and 1, 2, 3, 4, 12, and 18 hours after extubation. Owners evaluated their dogs’ appetite, activity, and wound soreness on postoperative days 2, 3, and 4.

Results—Dogs that received ketamine infusions had significantly lower pain scores 12 and 18 hours after surgery and were significantly more active on postoperative day 3 than dogs that received saline solution infusions.

Conclusions and Clinical Relevance—Results suggest that perioperative administration of low doses of ketamine to dogs may augment analgesia and comfort in the postoperative surgical period. (/Am Vet Med Assoc 2002;221:72–75)

Despite a great deal of recent attention, management of postoperative pain in animals is still 1 of the most challenging aspects of veterinary medicine. The 2 classes of drugs most often used in dogs to provide analgesia in the perioperative period are opioids such as morphine, oxymorphone, fentanyl, and butorphanol and nonsteroidal anti-inflammatory drugs (NSAID) such as carprofen and ketoprofen. Each of these drug classes has disadvantages such as dysphoria and respiratory depression (opioids) or gastrointestinal and renal toxicity (NSAID) that limit their usefulness in management of acute postoperative pain. Some painful procedures, such as forelimb amputations, are not as responsive as are hind limb procedures to certain ancillary analgesic techniques such as epidural administration of morphine. Therefore, clinicians continue to search for additional techniques or drugs that will improve pain management and patient comfort.

Ketamine (KET), an injectable anesthetic commonly used in many species of animals, is now receiving a great deal of attention in the human literature for its ability to decrease postoperative pain.1-3 Ketamine is a potent noncompetitive antagonist at N-methyl D-aspartate (NMDA) receptors in the spinal cord that are thought to be responsible for wind-up (exaggerated painful response to relatively innocuous stimuli following a primary injury).2 Thus perioperative administration of KET may prevent wind-up from occurring, thereby reducing postoperative pain. In humans, low (subanesthetic) doses of KET given by constant rate infusion (CRI) before and during surgery have improved postoperative analgesia and reduced the need for opioids in patients undergoing abdominal surgery, diskectomy, nephrectomy, and other types of surgery.1-4 The analgesic effects of KET in humans undergoing abdominal surgery persisted well beyond the expected duration of KET.1 These results suggest that KET may have beneficial effects on patient recovery long after the immediate postoperative period.

Ketamine has many desirable characteristics as an analgesic. It causes minimal cardiovascular depression, does not depress laryngeal protective reflexes, and depresses ventilation less than some other anesthetics or analgesics.5 Although KET can cause dysphoria or hallucinatory effects, in humans these undesirable effects do not seem to occur with the low doses used to produce analgesia.5

There is at least 1 report suggesting that a single subanesthetic dose of KET (2.5 mg/kg [1.1 mg/lb], IM) provided short-acting postoperative analgesia in dogs after ovariohysterectomy. To our knowledge, the efficacy of low-dose KET CRI for control of perioperative pain in dogs has not been investigated. On the basis of reports from the human literature, we decided to administer low-dose KET CRI to dogs undergoing forelimb amputation at Colorado State University’s Veterinary Teaching Hospital (CSU-VTH). Our hypothesis was that low-dose KET CRI would improve pain relief following forelimb amputation in dogs. Specifically, our goal was to compare indicators of postoperative pain and behavior, in an objective and blinded fashion, in dogs undergoing forelimb amputation,
with and without a low-dose KET CRI added to usual perioperative management.

**Materials and Methods**

**Dogs**—Dogs admitted to the CSU-VTH with osteosarcoma or other malignant tumors necessitating amputation of a forelimb were eligible for inclusion in the study; however, dogs with preexisting pathologic fractures or those scheduled for additional surgeries at the same time were excluded, as were dogs that were already receiving analgesic drugs. Informed consent was obtained from each dog’s owner before it was entered into the study protocol. This study was reviewed and approved by Colorado State University’s Animal Care and Use Committee.

**Pain score**—On the morning of surgery before any medications were given (baseline), each dog was evaluated for behavioral characteristics and pain indicators by use of a modified University of Melbourne Pain Scale (UMPS). Brieﬂy, this scale includes scores for both physiologic data (pupillary dilatation, heart rate, respiratory rate, arterial blood pressure, body temperature, and salivation) and behavioral characteristics (response to wound palpation, activity, mental status, posture, guarding, and vocalization). A score of 0 to 30 is possible, with increased scores indicative of greater pain. All evaluations were performed by 1 of 2 trained veterinary technicians or 1 of the authors (AEW). In all instances, the evaluator was blinded to the dog’s treatment throughout the study.

**Experimental protocol**—After baseline evaluation was completed, the dog was anesthetized for forelimb amputation by use of a standardized anesthesia protocol to minimize interanimal variability. The protocol consisted of administration of glycopyrrolate (0.01 mg/kg [0.005 mg/lb], SC) and morphine (1 mg/kg [0.45 mg/lb], SC) followed by IV catherization and induction of anesthesia with propofol (2 to 6 mg/kg [0.9 to 2.7 mg/lb], IV, to effect). After endotracheal intubation, anesthesia was maintained at an appropriate surgical plane with isoflurane in 100% oxygen. Dogs received lactated Ringer’s solution, approximately 10 ml/kg/h (4.5 ml/lb/h), IV, throughout anesthesia and surgery. Standard anesthesia monitoring included arterial blood pressure (direct or indirect), ECG, pulse oximetry, and capnography.

Dogs were assigned to receive either KET or physiologic saline solution (SAL; 0.9% NaCl) according to a random number table kept in the pharmacy. Only the pharmacist dispensing the KET or SAL was aware of which treatment each dog received. The study drug received from the pharmacy was diluted with physiologic SAL (1 part study drug with 9 parts SAL), resulting in a KET concentration of 10 mg/ml, which simplified precise dosing. After induction of anesthesia and before surgery began, either KET (0.5 mg/kg [0.23 mg/lb], IV) or a like volume of SAL was administered, followed immediately by starting either a KET CRI at 10 µg/kg/min or a SAL CRI at the same volume. Forelimb amputation was performed by use of standard techniques. The nerves of the brachial plexus were infiltrated with approximately 2 ml of 0.75% bupivacaine hydrochloride just prior to sectioning. The CRI of KET or SAL was continued at the same rate throughout surgery until the dog was transported to the critical care unit, at which time the CRI and isoflurane were discontinued. Once each dog had recovered from anesthesia sufﬁciently to be extubated, a bolus of fentanyl (2 µg/kg, IV) was given, and a fentanyl CRI was started at 2 µg/kg/h, IV. This fentanyl CRI could be increased or decreased according to the clinical judgment of the surgeon and the critical care nursing staff, who were also blinded to each dog’s KET or SAL treatment. As soon as possible after extubation, the dog was settled into a cage, and its KET or SAL CRI was resumed at a rate of 2 µg/kg/min KET or a like volume of SAL, IV. This CRI was continued at this rate until the dog was released from the critical care unit, generally 18 to 20 hours after surgery. All CRI were administered by syringe pump to ensure precise dosing. Administration of additional sedatives, tranquilizers, or analgesics was allowed if deemed appropriate for management of signs of pain or anxiety. Any such ancillary treatments were recorded in each dog’s record. If transdermal fentanyl patches were used, they were applied the day after surgery just before the dog went home. If morphine (PO) was prescribed, it was started the day after surgery.

**Pain assessment**—The evaluator reevaluated the dog by use of the UMPS at the time of extubation (time 0) and 1, 2, 3, 4, 12, and 18 hours after extubation. Dogs were generally discharged from the critical care unit approximately 18 to 20 hours after surgery, usually in the morning, and returned home with their owners that afternoon or the next day (second day after surgery). Once at home, each dog was evaluated by its owner for 3 days, beginning with the second day after surgery and ending with the fourth day. The owner’s evaluation consisted of daily numerical scores for appetite, personality, demeanor, and activity; and soreness of wound. Owners then mailed the completed evaluation form back to CSU-VTH.

**Statistical analyses**—Total UMPS scores, which were normally distributed, were compared by use of repeated-measures ANOVA, with fixed effects being treatment and time; post-hoc comparisons were made between least squares means by use of t tests. Owners’ scores for appetite, personality, demeanor, and activity; and soreness of wound on each of postoperative days 2, 3, and 4 were compared by the Fisher exact test. The Mann-Whitney U test was used to compare groups regarding fentanyl CRI dosage and incidence of use of adjunctive drugs such as acepromazine, xylazine or medetomidine, NSAID, transdermal fentanyl patches, and orally administered morphine. For all analyses, values of P < 0.05 were considered significant.

**Results**

Twenty-seven dogs were evaluated in the hospital for 18 hours after surgery; 13 received KET (5 Rottweilers, 3 Labrador Retrievers, 1 Golden Retriever, 1 mixed-breed, 1 Border Collie, 1 Siberian Husky, and 1 American Staffordshire Terrier), and 14 received SAL (2 Rottweilers, 1 Labrador Retriever, 1 Golden Retriever, 1 Flat-Coated Retriever, 5 mixed-breed, 1 Great Dane, 1 Alaskan Malamute, 1 German Shepherd Dog, and 1 Greyhound). Mean body weight was 39 kg (86 lb; range, 14 to 70 kg [31 to 154 lb]), and mean age was 8.5 years (range, 3 to 14 years). Mean surgery time for KET dogs was 114 minutes (range, 52 to 142 minutes), which was not significantly different from that for SAL dogs, 105 minutes (range, 60 to 146 minutes). Neither clinical anesthesia monitoring nor postanesthetic evaluations revealed any apparent cardiovascular or respiratory response to bolus or CRI administration of KET or SAL.

Dogs in the KET group had significantly lower total UMPS scores than dogs in the SAL group at 12 and 18 hours after extubation (P = 0.027 and 0.011, respectively; Table 1). Because of an unexpectedly large (but not significant) difference in UMPS scores between groups at baseline, an additional analysis was performed by use of ANCOVA with the covariate as the
Table 1—Mean (± SE) total University of Melbourne Pain Scale scores for dogs undergoing forelimb amputation, with and without adjustments for the difference at baseline. Dogs were given either saline (SAL; 0.9% NaCl) solution or ketamine (KET), administered by constant rate infusion baseline measurement. This analysis similarly revealed significantly lower adjusted UMPS scores in the KET group at 12 and 18 hours after extubation (P = 0.026 and 0.013, respectively). The owner of 1 dog in the SAL group did not return an evaluation form, so owner evaluations for only 26 dogs (13 KET, 13 SAL) were available for analysis. Dogs in the KET group had significantly better scores for personality, demeanor, and activity on the third postoperative day than dogs in the SAL group (P = 0.0113; Table 2). There were no significant differences between SAL and KET groups in owner-assigned appetite scores (mean values, 2.8 to 3.3) or wound soreness scores (mean values, 1.3 to 1.7).

Fentanyl CRI dosage was increased above 2 µg/kg/h (maximum dosage, 5 µg/kg/h [2.3 µg/lb/h]) in 10 dogs in the SAL group (mean, 3.07 µg/kg/h [1.4 µg/lb/h]) and 8 dogs in the KET group (mean, 3.15 µg/kg/h [1.43 µg/lb/h]), but there was no significant difference between groups. Likewise, there was no significant difference between groups in frequency of postoperative administration of acepromazine (0.01 to 0.02 mg/kg [0.005 to 0.009 mg/lb]), IV, administered to 3 dogs in the KET group and to 5 dogs in the SAL group), xylazine (0.05 mg/kg [0.02 mg/lb]), IV, administered to 1 dog in the KET group and to 2 dogs in the SAL group), or transdermal fentanyl patches (applied to 5 dogs in the KET group and to 6 dogs in the SAL group). Dogs in the KET group were slightly, but not significantly, less likely to receive NSAID (administered to 2 dogs in the KET group and to 7 dogs in the SAL group; P = 0.0126) or morphine (administered orally to 3 dogs in the KET group and to 9 dogs in the SAL group; P = 0.069) than were dogs in the SAL group.

Discussion
Results of the present study suggest that in dogs undergoing forelimb amputation, perioperative treatment with low doses of KET is associated with a slight improvement in comfort during the postoperative period, as evidenced by significantly lower UMPS scores at 12 and 18 hours and by significantly better activity scores on the third postoperative day.

Ketamine has long been known to have analgesic effects even at subanesthetic doses. Administration of KET before a noxious stimulus may induce a preemptive analgesic effect. The aim of preemptive analgesia is to prevent or minimize the development of a hyperexcitable state of CNS sensitization called wind-up. Spinal cord NMDA receptors are apparently involved in this hyperexcitability so their blockade by an NMDA-antagonist such as KET can prevent central sensitization from occurring and potentially abolish hypersensitivity after it is established. Several studies of human subjects have revealed that preemptive administration of small doses of KET is associated with a reduction in postoperative pain and opioid requirements.

The KET dosage selected for this study was the same as that recommended in a study of human surgical patients: 0.5 mg/kg IV bolus, 10 µg/kg/min during surgery, and 2 µg/kg/min after surgery. However, the dose requirement for KET may be considerably different for dogs than in humans, it is possible that the optimal analgesic dose of KET is approximately 5 times higher in dogs than in humans, is it possible that the optimal analgesic dose of KET for dogs is also higher than that used in the present study. Further investigation will be necessary to evaluate the analgesic efficacy of other KET dosages and infusion rates in dogs and other species. However, the dosage and infusion rate described in the present report have been shown in a previous study to achieve CSF concentrations of KET sufficient to bind NMDA receptors in isoflurane-anesthetized dogs. Therefore, the current findings of significantly lower UMPS scores and significantly better activity scores at certain times after forelimb amputation in dogs may be evidence for the NMDA-antagonist effects of KET. More normal activity in the KET dogs, though significant only on postoperative day 3, suggests that KET may convey a slight benefit long after the drug is eliminated; distribution and elimination half-lives for KET in dogs are reported to be 1.95 and 61.3 minutes, respectively. One possible explanation for the prolonged analgesic effect of KET may be its active metabolite, norketamine, which is also known to bind to NMDA receptors.

Table 2—Mean (± SE) values for owner-assigned scores for personality, demeanor, and activity on postoperative days 2, 3, and 4 in dogs given either SAL or KET

<table>
<thead>
<tr>
<th>Day</th>
<th>SAL (range)</th>
<th>KET (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>3.69 ± 0.13</td>
<td>3.62 ± 0.18</td>
</tr>
<tr>
<td></td>
<td>(3–4)</td>
<td>(2–4)</td>
</tr>
<tr>
<td>3</td>
<td>3.85 ± 0.15</td>
<td>3.23 ± 0.17</td>
</tr>
<tr>
<td></td>
<td>(3–5)</td>
<td>(2–4)</td>
</tr>
<tr>
<td>4</td>
<td>3.38 ± 0.21</td>
<td>3.08 ± 0.21</td>
</tr>
<tr>
<td></td>
<td>(2–4)</td>
<td>(2–4)</td>
</tr>
</tbody>
</table>

*Significant (P < 0.05) difference detected between SAL and KET groups.
The maximum possible UMPS score is 30. It has been suggested that a UMPS score of < 6 can be interpreted as an indication that postoperative pain is well controlled. According to that guideline, levels of analgesia, as measured by use of the UMPS score, were generally acceptable in both KET and SAL groups during the first 4 hours after forelimb amputation. However, by 12 and 18 hours after amputation, analgesia was apparently less satisfactory in the SAL group, with mean scores slightly > 6 (Table 1). At no time did any individual dog in the KET group have a UMPS score > 9. However, 5 dogs in the SAL group had UMPS scores of 10 to 15 at 1 or more times, usually at 12 and 18 hours. One possible explanation for these differences may be that the main effect of KET is not on primary pain but on the wind-up phenomenon, which prolongs or enhances pain long after the primary stimulus has ended. An alternative explanation for the apparently delayed onset of the KET benefit is that residual effects of anesthesia masked potential differences between KET and SAL groups early in the recovery period.

The small KET dosages reportedly used for perioperative analgesia in human patients have not caused psychotomimetic effects. Although dysphoria was evident in some dogs in our study, it was not necessarily associated with administration of KET. Fentanyl may also induce dysphoria. The 2 dogs that had the most dysphoria were a Siberian Husky and an Alaskan Malamute, northern breeds that clinical impression suggests are commonly subject to opioid-induced dysphoria. The Husky received KET, and the Malamute received SAL. Both dogs responded well to small doses of medetomidine (1 to 2 μg/kg, IV).

It is important to state that KET is not recommended as a primary analgesic but is more rationally used as an adjunct to other analgesics such as morphine or fentanyl. For that reason, our standard protocol included morphine as a preanesthetic and a fentanyl CRI in the immediate postoperative period. Because the dogs in this study were clinical patients undergoing major surgery, every effort was made to ensure that postoperative pain and anxiety were optimally managed and that the study protocol and UMPS scoring did not supplant clinical judgment. Therefore, fentanyl CRI rates could be adjusted as deemed appropriate by the attending surgeon or the critical care nursing staff, and ancillary treatments such as acepromazine, xylazine, or medetomidine were permitted. The application of clinical judgment by various personnel certainly increased variability and presumably reduced the chances of finding a significant treatment effect for KET. Acepromazine is a tranquilizer that reduces anxiety and dysphoria but does not induce analgesic effects. Xylazine and medetomidine are α2 agonist drugs that cause both sedation and analgesia. It is likely that administration of these ancillary drugs affected the dogs’ UMPS scores at certain times and possibly even their owners’ evaluation scores on subsequent days. However, the lack of significant differences between KET and SAL groups in frequency of administration of these drugs, the small number of dogs that received these drugs, and the small doses of drugs administered suggest that the effect, if any, would have been negligible. Comparison of the effects of KET and SAL treatments would certainly have been clearer without this clinical variability; nevertheless, a significant benefit was apparently associated with KET treatment.

Results of this study suggest that perioperative administration of low doses of KET to dogs undergoing forelimb amputation may augment analgesia and comfort in the postoperative period, with a slight benefit possibly continuing beyond the expected duration of KET itself. Further studies will be necessary to determine the optimal dosage of KET as well as to identify other procedures and species for which it may have benefit.

References