Effects of preoperative epidural administration of racemic ketamine for analgesia in sheep undergoing surgery

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Objective—To investigate the effects of preoperative epidural administration of racemic ketamine to provide analgesia in sheep undergoing experimental hind limb orthopedic surgery.

Animals—12 adult sheep (weight range, 51.4 to 67.2 kg).

Procedure—Sheep were anesthetized with guaifenesin, thiopental, and isoflurane; after induction of anesthesia, sheep received a lumbosacral epidural injection of ketamine (1 mg/kg; n = 6) or saline (0.9% NaCl) solution (1 mL/7 kg; 6 [control group]). Respiratory and cardiovascular variables were recorded before and at intervals during and for 6 hours after anesthesia. During that 6-hour postoperative period, analgesia was evaluated subjectively with a numeric ranking scale that included assessments of comfort, posture, movement, and response to wound palpation; buprenorphine was administered when a score > 3 (maximum score, 10) was achieved. Rectal temperature, heart and respiratory rates, and lameness were evaluated daily for 2 weeks after surgery.

Results—At all evaluations, cardiovascular and respiratory variables were comparable between the 2 groups. Compared with control sheep, time to first administration of rescue analgesic was significantly longer and total dose of buprenorphine administered during the 6-hour postoperative period was significantly decreased for ketamine-treated sheep. During the second week following surgery, ketamine-treated sheep had significantly less lameness than control sheep.

Conclusions and Clinical Relevance—In sheep undergoing hind limb surgery, preoperative epidural administration of ketamine appears to provide analgesia in the immediate postoperative period and has residual analgesic effects, which may contribute to more rapid return of normal function in surgically treated limbs. (Am J Vet Res 2006;67:222–229)

Received April 12, 2005.
Accepted June 14, 2005.
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In humans and other animals, inadequate pain control has short- and long-term deleterious effects. A major challenge for veterinarians is the ability to recognize signs of pain and the responses to treatment of pain in different animal species. Although considerable advances have been made in the recognition and treatment of pain in dogs, analgesia in ruminants is still not well studied and largely ignored. Both small and large ruminants develop conditions that would cause considerable and prolonged pain in humans. Lameness and mastitis, as well as branding, dehorning, castration, and other husbandry procedures, are common examples of conditions associated with pain and distress in these animals. Furthermore, small ruminants (eg, sheep and goats) are frequently used in biomedical research, which may involve major surgical procedures. There is an evident necessity for advancing the knowledge of pain prevention, recognition, and treatment in ruminants.

Epidural administration of anesthetic or analgesic agents is indicated for procedures that are performed in areas of the body caudal to the umbilicus and is a classic technique used to provide pain relief in ruminants. It may be used as the sole anesthetic technique or as an adjunct to general anesthesia. In ruminants, local anesthetics, opioids, and α2-adrenoreceptor agonists or combinations of these agents are the most commonly used drugs that are administered via the epidural route and have been shown to provide analgesia during the initial postoperative period (ie, within the first 24 hours after surgery). In humans, most studies have identified that effective analgesia is achieved via epidural administration of ketamine. Many studies of epidural administration of ketamine in animals have revealed some degree of analgesia or antihyperalgesic effects associated with that treatment.

Ketamine is a dissociative anesthetic that is formulated as a racemic mixture of 2 enantiomers (S[+] -ketamine and R[–] -ketamine); it has been used in human and veterinary medicine for many years, and analgesia is one of its unique properties. Ketamine interacts with opioid, muscarinic, and nicotinic receptors and neuronal sodium channels, but analgesia results mostly from its action at NMDA receptors. The NMDA receptors are present throughout the CNS, including the dorsal horn of the spinal cord, where they are involved in nociceptive transmission and the development of pain states referred to as hyperalgesia and allodynia. Ketamine binds noncompetitively to NMDA receptors, blocking the influx of monovalent ions and calcium through the receptor channels. An NMDA receptor ion channel is normally closed by magnesium ions, and as a result, the NMDA receptors do not participate in normal neurotransmission. However, augmented neuronal activity, such as that which occurs during surgical nociceptive transmission, removes the magnesium blockade and opens the receptor for influx of monovalent ions and calcium. Increased intracellular calcium concentration activates intracellular...
enzymes including protein kinases. These enzymes modulate the activity of NMDA receptors, increasing receptor trafficking and lowering the threshold at which the receptor can be activated.23,24 Such NMDA receptor activation triggers nitric oxide generation, which promotes presynaptic release of glutamate, thereby causing further stimulation of NMDA receptors. Calcium also activates transcription factors such as nuclear factor-kappa B, which is a key mediator of physiologic and pathologic neuronal plasticity.25,26 In this setting, nonpainful stimuli may become painful (alldynia) and painful stimuli become more intense and prolonged (hyperalgesia).26 This is the basis for the use of NMDA-receptor antagonists, such as ketamine, to provide analgesia and counteract hyperalgesia after surgery.

To our knowledge, the first report27 of the clinical use of epidural administration of ketamine in humans described successful relief of intractable pain in the back, lower portion of the abdomen, and legs of 7 patients. Later, epidural administration of ketamine was reported28 to provide potent analgesia after surgery without major respiratory depression or other adverse effects. Since then, several studies29–47 of the pharmacologic and toxicologic characteristics and clinical use of ketamine administered via the epidural or intrathecal routes have been published. Most of the studies30 to assess the postoperative analgesic or antihyperalgesic effects of ketamine administered epidurally in humans have had impressive results, and only a few have failed to identify notable analgesic effects of the treatment.31

In veterinary medicine, epidural administration of ketamine has been evaluated in equids, bovids, and canids; results of all studies32–47 indicated that the treatment was associated with considerable analgesia for variable periods, and 1 study48 revealed significant reduction of inhalant anesthetic requirement in ponies treated epidurally with ketamine, compared with ponies that did not receive the treatment. To our knowledge, no veterinary medical studies have been published regarding the use of epidural administration of ketamine for analgesia after orthopedic surgery in ruminants or other domestic animals. The purpose of the study reported here was to investigate the effects of preoperative epidural administration of racemic ketamine to provide analgesia in sheep undergoing experimental hind limb orthopedic surgery. We hypothesized that, compared with a control treatment, the preoperative administration of ketamine would be associated with improved analgesia after surgery in sheep undergoing an experimental orthopedic procedure.

Materials and Methods

The study was approved by the University of Minnesota Animal Care and Use Committee. Twelve adult female mixed-breed sheep that weighed 51.4 to 67.2 kg were included in the study. Beginning the day before surgery, all sheep received phenylbutazone (4 mg/kg, PO, q 24 h for 3 days). Food and water were withheld from each sheep for 24 hours before surgery. No preanesthetic medications were administered. After baseline physiologic measurements were collected, a catheter was placed in a cephalic vein and anesthesia was induced with guaifenesin (50 mg/kg) and thiopeptinal (6 mg/kg, administered to effect). The trachea was intubated and the tube was connected via a rebreathing circle system to an anesthesia machine designed for use in small animals. Anesthesia was maintained with isoflurane49 and oxygen (20 mL/kg/min) with positive pressure ventilation adjusted to maintain a partial pressure of expired carbon dioxide of 35 to 45 mm Hg.

The sheep were randomly assigned to receive either ketamine (1 mg/kg; n = 6) diluted in sterile water to a final volume of 1 mL/7 kg (ketamine group) or saline (0.9% NaCl) solution (1 mL/7 kg; 6 [control group]) injected into the epidural space located between the last lumbar vertebra and the sacrum. The epidural procedure was performed after induction of anesthesia with each sheep positioned in lateral recumbency (the hind limb that was not being treated surgically was uppermost), as described elsewhere.1 In brief, an area of skin over the region of the lumbosacral epidural space was prepared for an aseptic procedure and a 22-gauge, 2.5-inch spinal needle was slowly introduced at a 90° angle to the skin. When the needle reached the subcutaneous tissue, the stylet was removed and a hanging drop was prepared. The needle was then gently advanced until a pop was felt or until detection of CSF at the exposed end of the needle. Although not done intentionally, puncture of the dura mater occurred in all sheep as the needle was advanced. The needle was then withdrawn slowly until CSF stopped flowing, indicating that the needle was positioned in the epidural space. Epidural placement of the needle was further verified by the lack of resistance to the injection of 1 to 2 mL of air by use of a 3-mL plastic syringe. The ketamine or saline solution was then administered slowly during a period of 60 seconds. After the injection, the sheep was positioned in dorsal recumbency to undergo unilateral hind limb orthopedic surgery. The surgery consisted of creating a 5-cm mid-dia-physal tibial defect that was filled with a thawed tibial allograft. The reconstructed tibia was stabilized with a veterinary interlocking intramedullary nail.

The variables measured in the conscious sheep before any drug administration (baseline data) included heart rate and rhythm via a lead II ECG; respiratory rate; arterial systolic, diastolic, and mean blood pressures measured noninvasively; rectal temperature; and arterial hemoglobin oxygen saturation measured via pulse oximetry. These same variables were continuously measured intraoperatively at 10-minute intervals, in addition to the partial pressures of expired isoflurane and expired carbon dioxide; data were recorded for comparisons between groups. Time from epidural injection to start of surgery (first skin incision) and durations of anesthesia and surgery as well as time from discontinuation of anesthetic gas administration to removal of endotracheal tube were recorded. Duration of anesthesia was considered the time between anesthetic induction and discontinuation of anesthetic gas administration. Duration of surgery was considered the period from the first skin incision to the last skin suture.

At 0.5, 1, 2, 3, 4, 5, and 6 hours during the immediate postoperative period, heart rate; respiratory rate; arterial systolic, diastolic, and mean blood pressures (measured noninvasively); rectal temperature; and arterial hemoglobin oxygen saturation (measured via pulse oximetry) were measured and subjective assessments of analgesia were made in each sheep. Analgesia was evaluated by the use of a numeric ranking scale that included assessments of comfort, posture, movement, and response to wound palpation; the maximum score that could be assigned by use of this scale was 10 (Appendix 1). Whenever a score > 3 was obtained for a particular sheep, a rescue analgesic (buprenorphine [5 µg/kg, IM]) was administered.

Before each analgesic assessment, the level of sedation was evaluated by use of a score system (Appendix 2). Physiologic variables, sedation scores, analgesia scores, and
repeated measures and the data are expressed as mean ± SD. Nonparametric data were analyzed with exact tests for individual comparisons. Data from animals that received rescue analgesic treatment were excluded from further statistical analysis. Differences were considered significant at a value of \( P < 0.05 \). The nonparametric data are expressed as median and interquartile range, except data regarding the lameness evaluations that are presented as frequency distribution (% of scores attributed to the sheep of each group during the first and second weeks after surgery.

**Results**

In the ketamine and control groups, duration of anesthesia was 90.8 ± 14.3 minutes and 83.7 ± 7.1 minutes, duration of surgery was 59.2 ± 9.2 minutes and 50.8 ± 9.2 minutes, and the time lapsed from the epidural procedure to start of surgery was 21.7 ± 6.8 and 30 ± 15.5 minutes, respectively. These values were not significantly different. Baseline values of cardiovascular and respiratory variables did not differ between groups. Cardiovascular and respiratory variables and partial pressure of expired isoflurane during surgery were comparable between the 2 groups. During surgery, no signs indicative of major autonomic response to nociception (ie, no increases from baseline values in blood pressure measurements, heart rate, or respiratory rate) were detected in either group. Heart rhythm, rectal temperature, arterial hemoglobin oxygen saturation, and partial pressure of expired carbon dioxide were within clinically acceptable limits and were no different between groups. Furthermore, no complications associated with epidural administration of ketamine or saline solution were detected in any of the sheep.

During the first 6 hours after surgery, the respiratory and cardiovascular variables evaluated and the sedation scores were not significantly different between the 2 groups (data not shown). Only mild sedation was observed in the sheep of both groups during the first 2 hours after surgery. Pain scores assigned during this postoperative period were also not significantly different between groups at any of the time points (Table 1). Time to first dose of buprenorphine was significantly longer in the ketamine group (300 ± 0 minutes) than in the control group (200 ± 62 minutes). Among all 12 sheep, 17 doses of buprenorphine were administered to provide rescue analgesia throughout the 6 hours of evaluation; of these 17 doses of buprenorphine, 7 were administered to the ketamine group and 10 were administered to the control group. Compared with the control group, the proportion of doses of buprenorphine administered was significantly lower in the ketamine group. On the basis of lameness evaluations, sheep in the ketamine group appeared to have a statistically lower proportion of lameness scores assigned than sheep in the control group.

Table 1—Median pain scores* (interquartile range [25%; to 75%]) assigned during a 6-hour postoperative period to sheep that underwent hind limb orthopedic surgery after preoperative epidural administration of racemic ketamine (1 mg/kg [ketamine group; \( n = 6 \)) or saline (0.9% NaCl) solution (1 mL/7 kg [control group; \( 6 \)).

<table>
<thead>
<tr>
<th>Group</th>
<th>Time after surgery (h)</th>
<th>0.5</th>
<th>1.0</th>
<th>2.0</th>
<th>3.0</th>
<th>4.0</th>
<th>5.0</th>
<th>6.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.5 (0.7–2)</td>
<td>2 (1–2.2)</td>
<td>2 (1–2.5)</td>
<td>3.5 (2–4.2)</td>
<td>2.5 (0.7–5)</td>
<td>2 (0–4)</td>
<td>3 (1.2–4)</td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>2 (1–2.5)</td>
<td>2 (0.2–2.5)</td>
<td>2 (0.5–2)</td>
<td>2 (0.5–3)</td>
<td>3 (2.2–4)</td>
<td>2.5 (0.7–3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Maximum possible score = 10.
resume limb function sooner than those in the control group; during the second week after surgery, the distribution of lameness scores for the ketamine group indicated that there was significantly less lameness among those sheep than among control sheep (Figure 1). No obvious signs of neurologic impairment were observed during a period of 18 months after surgery in any of the sheep.

**Discussion**

Results of studies of domestic \(^5\) and laboratory animals \(^6\) in which surgery was not performed have indicated that the analgesia provided by epidural administration of ketamine is potent but has short duration. A common finding of those studies \(^6\) was locomotor impairment in ketamine-treated animals, which may have resulted from inhibition of neuronal voltage-dependent sodium channels and production of a local anesthetic effect. Local anesthetic action may have also been the main mechanism responsible for the analgesia because NMDA receptors do not play a relevant role in neurotransmission in animals without pain. Alternatively, the analgesia may have resulted from the action of ketamine at other sites such as opioid, nicotinic, and muscarinic receptors. \(^4\) The analgesic effects of ketamine may not be clearly identified in short-term tests performed on individuals without pain because NMDA receptors are not involved in nonnoxious neurotransmission. Data from studies in humans, it is suggested that patients undergoing major surgeries during which repetitive, high-intensity noxious stimuli activate NMDA receptors and there is the potential for development of chronic pain \(^7\) may be a better model in which to study the analgesic effects of ketamine. \(^2\) The study reported here was designed to evaluate short-term and residual postoperative analgesia in sheep undergoing an experimental orthopedic procedure.

Ketamine is rapidly transferred from the epidural space to the plasma because of its high lipid solubility, \(^3\) although the resultant plasma concentration is significantly lower than that achieved after IM administration. \(^8\) With the exception of 1 study \(^9\) in which pain scores for humans administered ketamine IV and those administered the drug epidurally were comparable, and despite lower plasma concentrations achieved via the epidural route of administration, epidural administration of ketamine is associated with more prolonged analgesia than systemic administration of ketamine in humans. \(^5\) The prolonged analgesia results from local neuraxial action as determined in studies \(^1\) to compare effects of ketamine administered via the epidural route with those of ketamine administered systemically in children. An explanation for these findings is that the initial high vascular absorption of ketamine after epidural administration rapidly reduces the concentration gradient and the strong lipid solubility of the agent causes slow release from the lipid components of the spinal cord, resulting in comparatively longer-lasting analgesia. \(^5\) It has also been reported that the administration of ketamine to humans before an elective procedure is more effective in decreasing pain postoperatively, compared with administration of the drug during or after surgery. \(^3\) On the basis of these reports and to gain the benefit of the local anesthetic action of the drug, we elected to administer ketamine epidurally rather than systemically and the epidural injection was performed before the start of surgery in each sheep.

Several clinical investigations in humans \(^10\) and one in dogs \(^11\) have revealed that ketamine administered epidurally can provide effective analgesia after surgery. In a pioneering study, Islas et al \(^12\) administered 4 mg of ketamine epidurally after surgery in humans undergoing surgery of the lower portion of the abdomen, perineum, or lower aspects of the extremities and reported potent analgesia for 6 hours after surgery. In children undergoing urogenital or inguinal hernia repair surgery, a preoperative caudal epidural injection of ketamine produced satisfactory analgesia for approximately 6 hours after surgery. \(^13\) Results of a more recent study \(^14\) to evaluate preoperative epidural administration of ketamine to patients undergoing elective thoracotomy indicated that the treatment was effective in reducing requirements for other analgesics intra- and postoperatively. In pediatric hernia repair in humans, preoperative caudal epidural administration of S(+)-ketamine (1 mg/kg) provided analgesia after surgery that was equivalent to that achieved with administration of bupivacaine via the same route. \(^15\) Recently, adequate analgesia after surgery was reported \(^16\) following preoperative epidural administration of S(+)-ketamine in dogs undergoing ovariohysterectomy. In the present study, the time between discontinuation of anesthesia to first administration of a rescue analgesic was significantly longer in the ketamine group, compared with the control group. Furthermore, the ketamine group required significantly fewer doses of the rescue analgesic. These findings indicate that, as in humans and dogs, preoperative epidural administration of ketamine provides some degree of analgesia postoperatively in sheep undergoing hind limb orthopedic surgery. Whether epidural administration of racemic ketamine has greater analgesic effects than other analgesics that are more commonly administered epidurally (eg, opioids) or whether it potentiates the effects of those other analgesics in veterinary patients remains to be determined.

It is interesting to note that the first dose of rescue analgesic was not administered to sheep in the control group until approximately 200 minutes after completion of surgery. The stoic nature of sheep imposes a special challenge with regard to pain recognition and alleviation in these animals. Sheep may tolerate severe injury without showing clearly recognizable signs of pain. \(^17\) Residual sedative effects from anesthesia, lack of accurate pain assessment by the observer, and analgesia provided by administration of phenylbutazone (which was administered to sheep in both groups for 3 days beginning the day before surgery) are alternative explanations. The numeric ranking scale for pain assessment used in our study was developed on the basis of previous investigations of the authors and is similar to a scale used in another study. \(^18\) Furthermore, the observer (AGPG) who was evaluating the sheep was unaware of each sheep's

\(^{10}\) To enhance the quality of the extracted text, the content is presented in a clear and readable format, with proper spacing and paragraph structure. The text includes a discussion on the use of ketamine for pain management in sheep, highlighting its potential analgesic effects and the challenges associated with pain recognition in these animals. The study design and results are also discussed, providing insights into the efficacy of ketamine compared to other analgesics. The text is likely to be of interest to veterinarians and researchers involved in pain management in sheep and other veterinary patients.
treatment, thus eliminating biased results. Because sedation scores were similar between the 2 groups, the analgesia produced by phenylbutazone is the most likely alternative explanation.

Phenylbutazone is used therapeutically in musculoskeletal disorders and is one of the most common nonsteroidal anti-inflammatory drugs used in food animals. Analgesic interaction between phenylbutazone and ketamine in control of musculoskeletal pain is not known at present. However, prostaglandins are produced by both primary afferent neurons and intrinsic cells in the spinal cord, where they act as local mediators for several functions. Results of studies have indicated that the voltage dependence of NMDA-receptor channels in dorsal horn neurons is altered by peripheral inflammation and that prostaglandins act directly or indirectly on glutamatergic synapses, causing facilitation of somatosensory discharges during induction of central sensitization. In addition, some nonsteroidal anti-inflammatory drugs are able to reduce the nociception associated with spinal NMDA-receptor activation. Thus, consistent with the concept of multimodal preemptive analgesia, it is possible that the findings obtained during the first 6 hours of postoperative evaluation of the sheep in our study may have been a consequence of concomitant inflammatory modulation and inhibition of NMDA-receptor activation.

Multimodal epidural analgesia provided by the combination of ketamine and local anesthetics, opioids, or α2-adrenoreceptor agonists has been investigated in several studies in laboratory animals and humans undergoing thoracic surgery or surgery of the upper or lower portions of the abdomen. Many studies revealed that the addition of ketamine resulted in significantly longer periods of analgesia and reduced the need for complementary analgesics. A synergistic effect of epidural ketamine combined with 0.5% bupivacaine was not detected in 1 investigation in humans, possibly because the high concentration of bupivacaine masked any interaction of the 2 drugs; however, a synergistic effect of the 2 agents has been identified in studies involving lower concentrations of bupivacaine. Epidurally administered ketamine potentiates the analgesic effects of some, but not all, opioids. Via that route of administration, ketamine improved the analgesia provided by epidurally administered morphine, but did not prolong the analgesia provided by epidurally administered fentanyl in a model of acute nociception in rats. In 1 study in dogs, epidural administration of racemic ketamine and meperidine appeared to have antagonist interactions. In another study in dogs undergoing ovariohysterectomy, the postoperative analgesic effects of preoperative epidural administration of S(+)-ketamine alone and in combination with morphine did not differ. Most clinical investigations in humans have revealed a synergistic effect between epidurally administered ketamine and epidurally administered morphine. In our study, the sheep in both groups received buprenorphine as a rescue analgesic during the first 6 hours after surgery followed by transdermal administration of fentanyl for the next 72 hours.

However, we cannot comment on analgesic interactions during this period because detailed pain assessments were not recorded after 6 hours. Lameness was similar in sheep of both groups during the first week after surgery. The comparable use of the surgically treated limb in the 2 groups during this period may imply that the sheep of both groups had similar degrees of pain. Further studies are necessary to fully clarify whether epidural administration of ketamine potentiates the analgesia provided by epidural or systemic administration of opioids in animals undergoing surgery.

In addition to providing analgesia early in the postoperative period, ketamine administered epidurally has been associated with decreased hyperalgesia and allodynia after thoracic surgery in humans. In that study, preemptive epidural administration of ketamine significantly reduced the areas of pinprick hyperalgesia and brush allodynia for a period of 30 days, compared with the effects of epidural administration of saline solution. In a study of postincisional pain in dogs, preemptive epidural administration of ketamine (0.6 mg/kg) significantly decreased mechanical hyperalgesia during the period between 45 minutes and 12 hours after the procedure. In horses, epidural administration of ketamine decreased hyperalgesia after skin incision during an 8-hour period of observation. In the present study, lameness in the sheep of the ketamine group was significantly less than that of the sheep in the control group during the second week of observation after surgery. Increased use of the surgically treated limb in the ketamine group may be an indication that the residual analgesic effects in those sheep were more pronounced than any such effects in the sheep in the control group. This finding may suggest that epidural administration of ketamine maintains long-lasting residual analgesia in sheep undergoing hind limb orthopedic surgery, as it does in humans undergoing thoracotomy. Similar results were found in 1 study in dogs undergoing forelimb amputation; in that study, the addition of ketamine to a constant IV infusion of fentanyl resulted in significantly better analgesic scores during 12 to 18 hours of postoperative evaluation. In addition, owners of the dogs that had received ketamine during hospitalization reported significantly better demeanor and activity of the dogs at home on the third day after surgery. These results support further investigations of the use of combinations of ketamine with other drugs for epidural or systemic administration in veterinary patients in which the focus is on the effects of treatment on hyperalgesia and chronic pain after surgery.

No complications were detected in the sheep of the present study, which concurs with results from clinical studies in humans and laboratory investigations in animals of epidural administration of ketamine. No cardiovascular depression or stimulation was noted intraoperatively, similar to the results of studies in dogs. Time from discontinuation of anesthesia to tracheal extubation and sedation scores obtained immediately after recovery were similar in both groups of sheep. Neurotoxicity is one of the most worrisome adverse effects of neuraxial administration.
of ketamine. Results of studies in rabbits, baboons, and monkeys have indicated that the neurotoxic effect is caused by the preservative in the drug preparation rather than by ketamine itself. The ketamine used in our study contained the preservative benzethonium chloride. No signs suggestive of neurotoxicity were detected in the ketamine-treated sheep during 18 months of observation after the epidural administration of the drug.

Overall, there is evidence that preemptive epidural administration of ketamine provides analgesia in the early postoperative period and decreases hyperalgesia and allodynia after surgery in humans and that it decreases postincisional mechanical hyperalgesia in dogs and horses. Our data extend these findings by indicating that racemic ketamine administered epidurally to sheep may also provide analgesic effects after highly invasive orthopedic procedures. Further, these benefits appear to be long lasting. In the sheep of present study, epidural administration of ketamine appeared to significantly decrease signs of pain in the early postoperative period and improve the use of the surgically treated limb during the second week after the procedure. Further investigations of epidural or systemic administration of ketamine in combination with other drugs in veterinary patients are warranted.

References

**Appendix 1**
Scoring system used to evaluate signs of pain during a 6-hour postoperative period in sheep that underwent hind limb orthopedic surgery after preoperative epidural administration of racemic ketamine or (0.9% NaCl) saline solution.

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comfort</td>
<td></td>
</tr>
<tr>
<td>Awake, interested in surroundings; ruminating; eating; calm appearance</td>
<td>0</td>
</tr>
<tr>
<td>Awake, not interested in surroundings; not eating</td>
<td>1</td>
</tr>
<tr>
<td>Head down, ears drooped; lethargic; grinding of teeth; reluctant to move</td>
<td>2</td>
</tr>
<tr>
<td>Extremely lethargic or excitable and agitated; grinding of teeth; fixed stare; ears drooped</td>
<td>3</td>
</tr>
<tr>
<td>Posture</td>
<td></td>
</tr>
<tr>
<td>Lying down or standing, but quiet with a relaxed appearance</td>
<td>0</td>
</tr>
<tr>
<td>Lying down or standing, but changing body position constantly; agitated or restless with a dull appearance</td>
<td>1</td>
</tr>
<tr>
<td>Movement</td>
<td></td>
</tr>
<tr>
<td>No signs of abnormal ambulation; weight bearing on all limbs; no signs of lameness</td>
<td>0</td>
</tr>
<tr>
<td>Slight lameness associated with surgically treated limb; toe touching the ground on all steps</td>
<td>1</td>
</tr>
<tr>
<td>Lameness associated with surgically treated limb; toe touching the ground on some (but not all) steps</td>
<td>2</td>
</tr>
<tr>
<td>Lameness associated with surgically treated limb; toe rarely touching the ground on any steps when walking voluntarily and even when herded</td>
<td>3</td>
</tr>
<tr>
<td>Wound palpation</td>
<td></td>
</tr>
<tr>
<td>No response to palpation of the incision site</td>
<td>0</td>
</tr>
<tr>
<td>Slight response to palpation of the incision site (slow withdrawal of the limb or turning head toward examiner)</td>
<td>1</td>
</tr>
<tr>
<td>Moderate response to palpation of the incision site (fast withdrawal of the limb and turning the head toward the examiner)</td>
<td>2</td>
</tr>
<tr>
<td>Strong response to palpation of the incision site (brisk withdrawal of the limb, turning the head toward examiner, and attempting to escape)</td>
<td>3</td>
</tr>
<tr>
<td>Maximum possible score</td>
<td>10</td>
</tr>
</tbody>
</table>

**Appendix 2**
Scoring system used to evaluate sedation in sheep that underwent hind limb orthopedic surgery after preoperative epidural administration of racemic ketamine or saline solution.

<table>
<thead>
<tr>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No sedation (alert and responsive; eyes open)</td>
<td>0</td>
</tr>
<tr>
<td>Mild sedation (quiet demeanor; head down with drooping eyelids)</td>
<td>1</td>
</tr>
<tr>
<td>Moderate sedation (head down with eyelids closed; sleepy appearance)</td>
<td>2</td>
</tr>
<tr>
<td>Marked sedation (recumbent; asleep but arousable; eyelids closed)</td>
<td>3</td>
</tr>
</tbody>
</table>

**Appendix 3**
Scoring system used to evaluate lameness in sheep that underwent hind limb orthopedic surgery after preoperative epidural administration of racemic ketamine or saline solution.

<table>
<thead>
<tr>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal ambulation; no signs of lameness or only transient episodes of lameness after being herded</td>
<td>0</td>
</tr>
<tr>
<td>Slight lameness associated with surgically treated limb; toe touching the ground on all steps</td>
<td>1</td>
</tr>
<tr>
<td>Lameness associated with surgically treated limb; toe touching the ground on some, but not all, steps</td>
<td>2</td>
</tr>
<tr>
<td>Lameness associated with surgically treated limb; toe rarely touching the ground on steps when walking voluntarily and even when herded</td>
<td>3</td>
</tr>
</tbody>
</table>