Evaluation of dexmedetomidine and ketamine in combination with opioids as injectable anesthesia for castration in dogs

Michele Barletta, DVM, PhD; Brenda R. Austin, DVM, MS, DACVS; Jeff C. Ko, DVM, MS, DACVA; Mark E. Payton, PhD; Ann B. Weil, MS, DVM, DACVA; Tomohito Inoue, DVM

Objective—To compare efficacy and cardiorespiratory effects of dexmedetomidine and ketamine in combination with butorphanol, hydromorphone, or buprenorphine (with or without reversal by atipamezole) in dogs undergoing castration.

Design—Prospective, randomized, split-plot, blinded study.

Animals—30 healthy client-owned sexually intact male dogs.

Procedures—Dogs (n = 10 dogs/group) were assigned to receive dexmedetomidine (15 µg/kg [6.82 µg/lb]) and ketamine (3 mg/kg [1.36 mg/lb]) with butorphanol (0.2 mg/kg [0.09 mg/lb]); DKBu, the same dosages of dexmedetomidine and ketamine with hydromorphone (0.05 mg/kg [0.023 mg/lb]; DKH), or the same dosages of dexmedetomidine and ketamine with buprenorphine (40 µg/kg [18.18 µg/lb]; DKBu). All drugs were administered as a single IM injection for induction and maintenance of anesthesia for castration. At conclusion of the surgery, 5 dogs in each treatment group received atipamezole (150 µg/kg [68.18 µg/lb], IM), and the remainder received saline (0.9% NaCl) solution IM. Cardiorespiratory variables and quality of anesthesia were assessed. Supplemental isoflurane was administered to the dogs when anesthesia was considered inadequate during surgery.

Results—All drug combinations rapidly induced anesthesia. Dogs were intubated within 10 minutes after injection. Supplemental isoflurane was needed during surgery in 1, 3, and 4 dogs in the DKBu, DKBu, and DKH groups, respectively. Dogs that received atipamezole had a significantly shorter recovery time. Some dogs in each group had bradycardia and hypoxemia with hypertension.

Conclusions and Clinical Relevance—DKBup was the most suitable injectable anesthetic combination used. Recovery was shortened by IM administration of atipamezole. There were minimal adverse effects in all groups. (J Am Vet Med Assoc 2011;238:1159–1167)

E xtensive studies have been conducted to evaluate the combined use of medetomidine and ketamine, with or without an opioid, as injectable anesthetic combinations in dogs. The advantages of combining medetomidine with ketamine and an opioid include predictable, rapid, and smooth induction and maintenance of anesthesia with excellent muscle relaxation and analgesia as well as smooth recovery from anesthesia. Furthermore, α₂-adrenoceptor agonists can be reversed to facilitate recovery, whereas postoperative analgesia remains from the opioid portion of the combination. Dexmedetomidine, a dextrorotary enantiomer of medetomidine, has replaced medetomidine in the veterinary market. The effects of substituting dexmedetomidine for medetomidine in established ketamine-opioid injectable protocols are unknown. In a recent literature search, only 1 study was identified in which investigators evaluated the use of dexmedetomidine and ketamine as an injectable anesthetic combination for radiography of the hip joints. Other dexmedetomidine-ketamine and opioid injectable anesthetic combinations have not been evaluated for short-duration surgical procedures. Because small animal practitioners commonly use injectable anesthetics alone or with inhalation anesthetics for short-duration surgical procedures, it is worthwhile to investigate the use of dexmedetomidine-ketamine-opioid–based anesthetic combinations for this purpose. For injectable anesthetic combinations, the IM route is most commonly used because of its ease and convenience of administration. For some clinical settings, such as high-volume, high-quality neutering clinics; shelter environments; or mobile field operations, IM administration provides major advantages over IV injection for short-duration surgical procedures because of ease of drug administration with minimal animal restraint while...
still allowing clinicians to achieve a rapid onset of and smooth rapid recovery from anesthesia. Various opioids, including butorphanol, hydromorphone, and buprenorphine, have been suggested for use in combination with dexmedetomidine and ketamine in dogs.8 However, it is unknown which opioid is optimal for use with a dexmedetomidine-ketamine combination for castration in dogs. Among these opioids, buprenorphine has a slower onset with a longer duration of action,8 whereas butorphanol and hydromorphone have a more rapid onset with a shorter duration of action. In another study,7 dogs sedated with dexmedetomidine (20 µg/kg [9.09 µg/lb]) and buprenorphine (15 µg/kg [6.82 µg/lb]) had a slower onset with a poorer quality of sedation and muscle relaxation than did dogs sedated with the same dose of dexmedetomidine and butorphanol (0.2 mg/kg [0.09 mg/lb]) for radiography of the hip joints. It is also unknown whether combining the opioids and ketamine with a lower dosage of dexmedetomidine (15 µg/kg) would be sufficient to rapidly induce anesthesia for castration. Furthermore, because IM administration of buprenorphine at a dosage of 15 µg/kg in combination with dexmedetomidine at a dosage of 20 µg/kg failed to induce sufficient sedation for radiography of the hip joints in the aforementioned study,7 it was hypothesized that an adjustment of the buprenorphine dosage to 40 µg/kg (18.18 µg/lb) in combination with dexmedetomidine and ketamine would be sufficient for providing anesthesia for castration in the study reported here. It was further hypothesized that all 3 dexmedetomidine-ketamine-opioid combinations would rapidly induce anesthesia for castration.

Atipamezole is a specific antagonist for dexmedetomidine and has been approved for reversing dexmedetomidine in dogs.8 Although there is an analgesic advantage to not reversing dexmedetomidine after a surgical procedure, the sedative effect associated with such analgesia may prolong the recovery time and impede maintenance of body temperature. On the other hand, antagonizing the dexmedetomidine-ketamine combination too early may allow lingering ketamine effects to remain dominant and cause a difficult recovery from anesthesia. It was hypothesized in the study reported here that the use of atipamezole for reversing dexmedetomidine combined with a lower dose of ketamine would shorten the duration of anesthesia with minimal adverse effects.

Therefore, the objectives of the study reported here were to compare the anesthetic efficacy and cardiorespiratory effects of dexmedetomidine and ketamine in combination with each of 3 opioids (butorphanol, hydromorphone, and buprenorphine) for elective castration in dogs and to evaluate the quality and speed of recovery from anesthesia when atipamezole was used to reverse the dexmedetomidine-ketamine-opioid combination after castration.

Materials and Methods

Animals—Thirty healthy client-owned sexually intact male dogs were enrolled in the study. The dogs were between 2 and 60 months of age (median, 12 months). Body weight of each dog was between 2.3 and 33.8 kg (5.06 and 74.36 lb), with a median weight of 12 kg (26.4 lb). Dogs were considered to be healthy on the basis of results of physical examination, medical history, and basic hematologic tests (PCV and concentrations of total protein, BUN, and blood glucose). Owner consent was obtained for inclusion of each of the dogs in the study. The study was approved by the Purdue University Animal Care and Use Committee.

Experimental procedure—The study was conducted as a blinded, randomized, split-plot design. The 30 dogs were assigned via a randomization procedure (drawing a number from a hat for assigning treatment groups and dog identification) to 3 treatment groups (n = 10 dogs/group). All 3 treatment groups received an IM injection that contained dexmedetomidine8 (15 µg/kg) and ketamine hydrochloride8 (3 mg/kg [1.36 mg/lb]) as well as an opioid; dogs in the DKBut group received butorphanol8 (0.2 mg/kg), dogs in the DKB group received hydromorphone8 (0.05 mg/kg [0.23 mg/lb]), and dogs in the DKBup group received buprenorphine8 (40 µg/kg). Within each treatment group, dogs then were allocated to receive an IM injection (saline [0.9% NaCl] solution [n = 5] or atipamezole1 [150 µg/kg [68.18 µg/lb]; 5] to reverse dexmedetomidine) at the completion of surgery. Thus, there were 6 groups (5 dogs/group), with saline solution and atipamezole as the split-plot factor. Drug dosages were derived on the basis of the clinical experience of the authors.

Food (but not water) was withheld from dogs for 4 to 12 hours before anesthesia and surgery. Duration of the food withholding was based on age of the dogs, with food withheld from mature dogs for 12 hours but withheld from extremely young dogs (ie, < 3 months old) for only 4 hours to reduce the risk of hypoglycemia. After the physical examination was completed, dogs were placed in cages and allowed to acclimate to the environment for at least 2 hours prior to anesthesia. Heart rate, respiratory rate, indirect blood pressure, and rectal temperature were recorded at baseline (5 minutes prior to IM administration of any drug combination).

Separate syringes were used to remove each of the drugs from their respective bottles; all drugs were mixed in the same syringe immediately prior to IM administration. Time of drug administration (ie, DKBut, DK, or DKBup) was designated as time 0. All drugs were administered in the right or left quadriceps femoris muscle. Carprofen4 (4 mg/kg [1.82 mg/lb]) was administered SC to each dog immediately before conclusion of the surgery. All surgeries were performed by an experienced surgeon (BRA). Both the surgeon and anesthetists were blinded to the treatments administered to each dog.

Cardiorespiratory monitoring—Six minutes after drug administration, heart rate and respiratory rate were determined via auscultation, SpO2 was measured by use of a pulse oximeter,9 blood pressure was noninvasively measured by use of an oscillometric device,10 PETCO2 was measured with a mainstream capnograph,1 and rectal temperature was recorded. The PETCO2 was measured only after dogs were intubated. The same variables were measured and recorded at 10 minutes and at 5-minute intervals thereafter until the dogs received atipamezole.
(approx 35 minutes after drug injection) or recovered spontaneously from anesthesia. An ECG was continuously monitored until surgery was completed. The dogs were allowed to breathe room air. If the SpO₂ was < 90% during anesthesia, supplemental 100% oxygen was provided until the SpO₂ was > 90%.

Monitoring of anesthesia and analgesia—Intervals from injection of the anesthetic (time 0) to the onset of sedation, lateral recumbency, and completion of endotracheal intubation were recorded. Investigators were allotted 10 minutes from the time of drug administration to perform endotracheal intubation. During these 10 minutes, 3 attempts were allowed for endotracheal intubation. If the dog could not be intubated during the 10-minute period, isoflurane in 100% oxygen was provided via a face mask to facilitate endotracheal intubation. After a dog was intubated, administration of isoflurane in 100% oxygen was terminated. Ease of endotracheal intubation was scored in accordance with defined criteria on a scale of 1 to 3 (1 = difficult intubation, tube cannot be retained, tight jaw tone accompanied by chewing motion, and strong tongue withdrawal; 2 = easy intubation with slight coughing or swallowing reflex following intubation but no gagging reflex, relaxed jaw tone, no chewing motions, and slight tongue withdrawal; or 3 = rapidly becomes anesthetized, good muscle relaxation, and intubation easily achieved without coughing or tongue withdrawal). Once intubated, the endotracheal tube was provided via a face mask to facilitate endotracheal intubation.

### Table 1

<table>
<thead>
<tr>
<th>Group*</th>
<th>Intubation score</th>
<th>Sedation-anesthesia score$</th>
<th>Recovery score$</th>
<th>Postoperative pain score</th>
<th>No. of dogs requiring oxygen¶</th>
<th>No. of dogs requiring isoflurane#</th>
</tr>
</thead>
<tbody>
<tr>
<td>DKBup-A</td>
<td>3.0 ± 0.0</td>
<td>4.0 ± 0.0</td>
<td>4.0 ± 0.0</td>
<td>1.0 ± 0.0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>DKBup-S</td>
<td>2.8 ± 0.2</td>
<td>4.0 ± 0.0</td>
<td>4.0 ± 0.0</td>
<td>1.0 ± 0.0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>DKBup-A</td>
<td>2.6 ± 0.2</td>
<td>4.0 ± 0.0</td>
<td>4.0 ± 0.0</td>
<td>1.0 ± 0.0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>DKBup-S</td>
<td>2.6 ± 0.2</td>
<td>4.0 ± 0.0</td>
<td>4.0 ± 0.0</td>
<td>1.0 ± 0.0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>DKBup-A</td>
<td>2.8 ± 0.2</td>
<td>4.0 ± 0.0</td>
<td>4.0 ± 0.0</td>
<td>1.0 ± 0.0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>DKBup-S</td>
<td>2.8 ± 0.2</td>
<td>4.0 ± 0.0</td>
<td>4.0 ± 0.0</td>
<td>1.0 ± 0.0</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

*There were 5 dogs in each of the 6 groups. All dogs received dexmedetomidine (15 µg/kg [8.82 µg/lb]) and ketamine (3 mg/kg [1.36 mg/lb]). In addition, dogs in group DKBup received buprenorphine (40 µg/kg [18.18 µg/lb]), dogs in group DKBup received butorphanol (0.2 mg/kg [0.09 mg/lb]), and dogs in group DKBup received hydromorphone (0.05 mg/kg [0.023 mg/lb]). Dogs were administered atipamezole (150 µg/kg [68.18 µg/lb], IM [All] or an equivalent volume of saline (0.9% NaCl) solution IM (SI). Endotracheal intubation was scored on a scale of 1 to 3 (1 = difficult intubation, tube cannot be retained, tight jaw tone accompanied by chewing motion, and strong tongue withdrawal; 2 = easy intubation with slight coughing or swallowing reflex following intubation but no gagging reflex, relaxed jaw tone, no chewing motions, and slight tongue withdrawal; or 3 = rapidly becomes anesthetized, good muscle relaxation, and intubation easily achieved without coughing, gagging, or tongue withdrawal). Anesthesia was scored on a scale of 0 to 4 (0 = active, aware of the surrounding environment, and minimal sedation; 1 = mild to moderate sedation with reduced activity and does not assume sternal or lateral recumbency; 2 = moderate sedation, mildly aware of the surrounding environment, and sternal recumbency; 3 = profound sedation, eyes droopy, head down, inactive, assumes sternal or lateral recumbency, tight jaw tone, and unable to be intubated; and 4 = rapid smooth induction of anesthesia, no movement, rapidly assumes lateral recumbency with good muscle relaxation and loose jaw tone, and easily intubated). Recovery from anesthesia was scored on a scale of 1 to 4 (1 = prolonged struggling, unresponsive; 2 = easy intubation with slight struggling that results in increased metabolism; 3 = some struggling, requires some assistance to stand, unable while standing, unable to maintain balance, and some signs of drug carryover effects; 4 = dog assumes sternal recumbency with little or minimal struggling, and minimal signs of drug carryover effects; and 4 = dog assumes sternal recumbency with little or minimal struggling, stands and walks with minimal effort, and no signs of drug carryover effects). Signs of pain were scored on a scale of 1 to 5 (1 = minimal pain = relaxed, resting comfortably, no vocalizing, moves freely, calm or asleep, and responds to voice and stroking; 2 [faint pain] = minimal agitation, resting calmly, barely noticeable pain, some position changes, and respondents to calm voice and stroking; 3 [mild pain] = mild agitation, some position changes, responds to calm voice and stroking, some salivation, and occasional vocalization; 4 [moderate pain] = moderate agitation, vocalization, excessive salivation, some vomiting, muscle trembling, frequent position changes, some thrashing, and responsiveness to painful pinch or tongue withdrawal; 5 [severe pain] = severe agitation, vomiting, defecation, vocalization, excessive salivation, head tossing, violent thrashing, does not respond to calm voice and stroking, and may require manual restraint to prevent injury). If the SpO₂ was < 90% during anesthesia, supplemental 100% oxygen was provided until the SpO₂ was > 90%. A dog displayed signs of inadequate anesthesia if the anesthetist judged there was an inadequate plane of anesthesia; thus, isoflurane in oxygen was administered until an adequate plane of anesthesia was achieved.

### Table 2

<table>
<thead>
<tr>
<th>Group*</th>
<th>Onset of sedation (min)</th>
<th>Lateral recumbency (min)</th>
<th>Start of surgery (min)</th>
<th>Duration of surgery (min)</th>
<th>Duration of endotracheal intubation (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DKBup-A</td>
<td>1.6 ± 0.4</td>
<td>3.4 ± 1.0</td>
<td>24.0 ± 0.4</td>
<td>16.0 ± 0.8</td>
<td>36.2 ± 0.7*</td>
</tr>
<tr>
<td>DKBup-S</td>
<td>2.6 ± 0.7</td>
<td>5.0 ± 0.7</td>
<td>22.2 ± 0.9</td>
<td>19.4 ± 1.5</td>
<td>77.4 ± 9.8*</td>
</tr>
<tr>
<td>DKBup-A</td>
<td>2.8 ± 0.2</td>
<td>4.4 ± 0.4</td>
<td>19.4 ± 0.8</td>
<td>17.0 ± 1.6</td>
<td>35.6 ± 2.3*</td>
</tr>
<tr>
<td>DKBup-S</td>
<td>3.8 ± 1.9</td>
<td>5.4 ± 2.2</td>
<td>24.8 ± 2.6</td>
<td>18.8 ± 1.9</td>
<td>52.6 ± 9.5*</td>
</tr>
<tr>
<td>DKBup-A</td>
<td>3.0 ± 0.8</td>
<td>6.0 ± 1.7</td>
<td>22.6 ± 1.8</td>
<td>18.8 ± 1.6</td>
<td>39.0 ± 2.4*</td>
</tr>
<tr>
<td>DKBup-S</td>
<td>2.2 ± 0.2</td>
<td>4.0 ± 1.0</td>
<td>22.8 ± 1.9</td>
<td>17.0 ± 2.1</td>
<td>38.6 ± 3.6**</td>
</tr>
</tbody>
</table>

*Within a column, values with different superscript letters differ significantly (P < 0.05). See Table 1 for remainder of key.
was allowed to remain in place until the surgery was complete and the dog began to cough and gag against the tube during recovery from anesthesia. At that time, the endotracheal tube was removed and the total duration of intubation was recorded.

Other variables recorded included the interval from injection of anesthetics to the beginning of surgery and the total duration of the surgical procedure. To compare quality of the injectable anesthesia, we attempted to standardize all procedures. We allowed 10 minutes from anesthesia injection to induction, 10 minutes for completion of endotracheal intubation, 10 minutes for surgical preparation and draping, and 10 minutes for the castration.

The overall quality of anesthesia and quality of recovery were graded according to defined criteria. Overall quality of sedation-anesthesia was scored on a scale of 0 to 4 (0 = active, aware of the surrounding environment, and minimal sedation; 1 = mild sedation with reduced activity and does not assume sternal or lateral recumbency; 2 = moderate sedation, mildly aware of the surrounding environment, and sternal recumbency; 3 = profound sedation, eyes droopy, head down, inactive, assumes sternal or lateral recumbency, tight jaw tone, and unable to be intubated; and 4 = rapid smooth induction of anesthesia, no movement, rapidly assumes lateral recumbency with good muscle relaxation and loose jaw tone, and easily intubated). Overall quality of recovery from anesthesia was scored on a scale of 1 to 4 (1 = prolonged struggling, unable to stand without assistance, hyperkinesis in response to manual assistance, and increased rectal temperature associated with increased struggling that results in increased metabolism; 2 = some struggling, repeated attempts to stand, requires assistance to stand, unstable while walking, unable to maintain balance, and some signs of drug carryover effects [eg, muscle trembling, salivation, head shaking, vocalization, or defecation]); 3 = some struggling, requires some assistance to stand, able to maintain balance once standing, and minimal signs of drug carryover effects; and 4 = dog assumes sternal recumbency with little or minimal struggling, stands and walks with minimal effort, and no signs of drug carryover effects).

During surgery, if a dog displayed signs of inadequate anesthesia (including increases in heart or respiratory rates or purposeful movement related to surgical stimulation) or the anesthetist judged there was an inadequate plane of anesthesia, then isoflurane in 100% oxygen was administered until an adequate plane of anesthesia was achieved. When the dog reached a stable plane of anesthesia, the end-tidal isoflurane concentration was recorded via an an-

Figure 1—Mean ± SEM heart rate for dogs (n = 5 dogs/group) after a single IM injection of various combinations of anesthetic drugs for castration, which was followed by administration of atipamezole or saline (0.9% NaCl) solution at the conclusion of surgery. All dogs received dexmedetomidine (15 µg/kg [6.82 µg/lb]) and ketamine (3 mg/kg [1.36 mg/lb]). In addition, dogs in group DKBup received buprenorphine (40 µg/kg [18.18 µg/lb]), dogs in group DKBut received butorphanol (0.2 mg/kg [0.09 mg/lb]), and dogs in group DKH received hydromorphone (0.05 mg/kg [0.023 mg/lb]). Time of administration of the anesthetic combination was designated as time 0. Dogs received an IM injection of atipamezole (150 µg/kg [68.18 µg/lb]; A) or an equivalent volume of saline solution (S) at the conclusion of surgery (arrow). Baseline heart rate was obtained at –5 minutes. Duration of anesthesia induction and surgical preparation (ie, induction), surgery, and recovery from anesthesia are indicated at the bottom of the figure. *Within a time point, value differs significantly (P < 0.05) from the values for the other treatment groups.

Figure 2—Mean ± SEM values for mean arterial blood pressure in dogs (n = 5 dogs/group) after a single IM injection of various combinations of anesthetic drugs for castration, which was followed by administration of atipamezole or saline solution at the conclusion of surgery. See Figure 1 for remainder of key.
esthetic agent monitor, and isoflurane was then discontinued. If the dog returned to a lighter plane of anesthesia, then the isoflurane in 100% oxygen again was administered. The duration of supplementation with isoflurane was recorded. The number of dogs in each group that received supplemental isoflurane was recorded.

Recovery from anesthesia—Once castration was complete, atipamezole or the same volume of saline solution was administered IM to the dogs. Time required for dogs to achieve sternal recumbency or to maintain a standing position after administration of atipamezole or saline solution was recorded. Dogs were placed on circulating heating blankets during recovery to maintain a rectal temperature of at least 36.7°C (98°F).

Dogs were observed for signs of pain during recovery. Pain behavior was scored in accordance with defined criteria. Signs of pain were scored on a scale of 1 to 5 (1 [minimal pain] = relaxed, resting comfortably, no vocalizing, moves freely, calm or asleep, and responds to calm voice and stroking; 2 [faint pain] = minimal agitation, resting calming, barely noticeable pain, some position changes, and responds to calm voice and stroking; 3 [mild pain] = mild agitation, some position changes, responds to calm voice and stroking, some salivation, and occasional vocalization; 4 [moderate pain] = moderate agitation, vocalization, excessive salivation, some vomiting, muscle trembling, frequent position changes, some thrashing, and responds slightly to calm voice and stroking; and 5 [severe pain] = severe agitation, vomiting, defecation, vocalization, excessive salivation, head tossing, violent thrashing, does not respond to calm voice and stroking, and possibly requires manual restraint to prevent injury). An additional dose of the same opioid that had been used for anesthesia was administered to dogs that had signs of pain during the recovery period.

Statistical analysis—All data were analyzed with a commercial statistical program. An ANOVA with a mixed-effects model was used to detect significant differences attributable to treatments. For significant results via the ANOVA, pairwise t tests were performed to determine differences between treatments. All data were reported as mean ± SEM. Significance was set at P < 0.05.

Results

Anesthesia quality—All dogs completed the study and recovered from anesthesia without complications. Overall, there were no significant differences in endotracheal intubation, anesthesia, pain, and recovery scores among treatment groups (Table 1). The mean interval from drug administration until onset of sedation ranged from 1.6 to 3.6 minutes and was followed by a smooth induction of anesthesia. Dogs became laterally recumbent within 4 to 6 minutes after the single IM injection of each anesthetic combination (Table 2).
The interval from anesthetic administration until the start of surgery (ie, skin incision) was approximately 20 minutes. There were no significant differences in the intervals from injection of the anesthetic combinations to onset of sedation, assumption of lateral recumbency, and the start of surgery, and there was no significant difference in the duration of surgery.

For all dogs, except for 1 dog in the DKH group, endotracheal intubation was easily achieved between 3 and 6 minutes after drug injection. That dog was only moderately sedated at 10 minutes after DKH injection, and thus, endotracheal intubation was not possible. Anesthesia in that dog was then induced with isoflurane administered via a face mask to enable endotracheal intubation. Additional administration of supplemental isoflurane was not necessary to perform surgery on that dog.

One, 3, and 4 dogs that received DKBup, DKBut, and DKH, respectively, had signs consistent with a light plane of anesthesia during surgical stimulation. Supplemental isoflurane was administered to maintain a surgical plane of anesthesia; the isoflurane percentages used were relatively low (between 0.5% and 1.0%). For the dog in the DKBup group, the interval from anesthetic injection until administration of supplemental isoflurane and the duration of isoflurane administration were 26 and 6 minutes, respectively. For the 3 dogs in the DKBut group, the interval from anesthetic injection until administration of supplemental isoflurane was 23, 28, and 33 minutes, respectively, and the duration of isoflurane administration was 10, 6, and 7 minutes, respectively. For the 4 dogs in the DKH group, 1 was the aforementioned dog that required isoflurane administered via a face mask to enable endotracheal intubation; the duration of isoflurane for that dog was 1 minute. For the other 3 dogs in the DKH group, the interval from anesthetic injection until administration of supplemental isoflurane was 23, 24, and 25 minutes, respectively, and the duration of isoflurane administration was 10, 5, and 2 minutes, respectively. Thus, the duration for administration of supplemental isoflurane was relatively short (between 1 and 10 minutes) for all dogs. Four of these dogs subsequently received atipamezole after conclusion of the surgery, and the other 4 dogs received saline solution.

Cardiorespiratory function from anesthesia induction until conclusion of surgery (0 to 35 minutes after drug administration)—Heart rate decreased significantly from the baseline value after anesthetic administration in all treatment groups. The range of changes in heart rates for specific dogs within each treatment group was calculated. Heart rate decreased 22% to 53%, 30% to 51%, and 32% to 59% of the baseline values, respectively, during the first 35 minutes after DKBup, DKBut, and DKH injection. Bradycardia was detected in DKBup dogs at 25 minutes (mean ± SEM, 36.8 ± 8.4 beats/min) and in DKBut dogs at 10 minutes (mean ± SEM, 94.6 ± 8.2 beats/min). Bradycardia (between 42.5 ± 2.8 beats/min and 59.4 ± 14.2 beats/min) was more pronounced and had a longer duration in the DKH-treated dogs and developed between 15 and 35 minutes after drug administration. Mean heart rate was significantly higher in DKBup dogs than in DKBut or DKH dogs during the first 35 minutes of anesthesia (Figure 1). Bradycardia and sinus arrhythmias were the only cardiac arrhythmias detected during the study.

Mean arterial blood pressure had a biphasic pattern, with an initial mild increase of 12% to 18%, 8% to 23%, and 15% to 18% from the baseline values during the first 10 minutes for the DKBup, DKBut, and DKH groups, respectively. After this time, mean arterial blood press-

![Figure 5](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3220046/figure/5/)

**Figure 5**—Mean ± SEM SpO₂ for dogs (n = 5 dogs/group) after a single IM injection of various combinations of anesthetic drugs for castration, which was followed by administration of atipamezole or saline solution at the conclusion of surgery. See Figure 1 for remainder of key.

<table>
<thead>
<tr>
<th>Group*</th>
<th>Heart rate (beats/min)</th>
<th>Systolic arterial blood pressure (mm Hg)</th>
<th>Mean arterial blood pressure (mm Hg)</th>
<th>Diastolic arterial blood pressure (mm Hg)</th>
<th>Respiratory rate (breaths/min)</th>
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</thead>
<tbody>
<tr>
<td>DKBup-A</td>
<td>109.3 ± 19.2*</td>
<td>97.0 ± 6.1</td>
<td>81.2 ± 4.1</td>
<td>68.0 ± 4.2</td>
<td>25.8 ± 5.3</td>
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<tr>
<td>DKBup-S</td>
<td>62.0 ± 8.1*</td>
<td>117.0 ± 7.1</td>
<td>89.8 ± 6.3</td>
<td>76.0 ± 6.3</td>
<td>17.8 ± 3.2</td>
</tr>
<tr>
<td>DKBup-A</td>
<td>86.8 ± 13.5</td>
<td>122.7 ± 20.1</td>
<td>90.7 ± 18.0*</td>
<td>74.5 ± 17.7*</td>
<td>14.2 ± 2.0</td>
</tr>
<tr>
<td>DKBup-S</td>
<td>64.4 ± 17.6</td>
<td>133.8 ± 10.4</td>
<td>110.2 ± 8.9*</td>
<td>98.6 ± 9.1*</td>
<td>20.0 ± 3.7</td>
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<tr>
<td>DKBut-A</td>
<td>49.4 ± 14.1</td>
<td>118.4 ± 13.5</td>
<td>96.4 ± 7.0</td>
<td>71.4 ± 5.0</td>
<td>17.8 ± 3.0</td>
</tr>
<tr>
<td>DKBut-S</td>
<td>42.5 ± 2.8</td>
<td>122.7 ± 10.2</td>
<td>95.3 ± 10.3</td>
<td>81.2 ± 10.3</td>
<td>20.3 ± 4.2</td>
</tr>
</tbody>
</table>

*See Tables 1 and 2 for key.

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**Table 3**—Mean ± SEM values for cardiovascular variables obtained 5 minutes after atipamezole or saline solution was administered IM at the conclusion of surgery in dogs that received a single IM injection of various combinations of anesthetic drugs for castration.
Hypoxemia developed within the first 15 minutes after drug administration, and supplemental oxygen was provided for a mean ± SEM of 13.5 ± 5.8 minutes, 14.4 ± 11.1 minutes, and 12.8 ± 7.0 minutes for dogs in the DKBup, DKBut, and DKH groups, respectively. All dogs responded to supplemental administration of 100% oxygen with an increase and maintenance of SpO₂ at > 90% (Figure 5).

Cardiovascular function during recovery from anesthesia, with and without atipamezole treatment—Heart rate decreased further during the recovery period to 75%, 70%, and 64% of the baseline values for the 5 dogs that received saline solution in the DKBup, DKBut, and DKH groups, respectively. Mean arterial blood pressure decreased further during the recovery period (decrease of 35%, 15%, and 2% from the baseline values) for the 5 dogs that received saline solution in the DKBup, DKBut, and DKH groups, respectively. Significantly lower heart rates with significantly higher blood pressures were detected between dogs treated with saline solution and atipamezole at 5 minutes after administration (Table 3). In general, heart rates remained low (37 to 60 beats/min), and mean blood pressures remained relatively high (87 to 120 mm Hg) during recovery in all dogs treated with saline solution (Figure 1). Sinus arrhythmias were more pronounced and frequent during recovery than during the preceding 35 minutes. Bradycardia and sinus arrhythmia were the only cardiac arrhythmias detected in the dogs treated with saline solution.

Rectal temperature was maintained between 36.4 and 39.4°C (97.5° and 103.0°F) for all dogs throughout the study (Figure 6). There was no significant difference among treatment groups with regard to rectal temperature.

Speed of recovery and recovery quality—Atipamezole administration significantly decreased the duration of recovery in all treated dogs (Table 4). All dogs that received atipamezole were able to achieve sternal recumbency within 6 minutes after IM injection of atipamezole and maintained a standing position within 10 minutes after IM injection of atipamezole. In contrast, dogs that received saline solution were not able to stand until at least 30 to 85 minutes after IM administration of the saline solution. Dogs in the DKBup group that received saline solution had a longer recovery time than did dogs in the atipamezole-treated groups.

![Figure 6](image-url)
dogs in the DKBut and DKH groups that received saline solution. Three dogs in the DKBup group that received saline solution were not able to stand until 90, 100, and 135 minutes after IM injection, respectively.

Despite the reversal of dexmedetomidine with atipamezole, no dissociative carryover drug effects (eg, muscle trembling, salivation, head shaking, vocalization, or defecation) were detected after atipamezole administration. None of the dogs had signs of pain or required rescue pain medication during or after recovery from surgery.

**Discussion**

Analysis of results of the study reported here revealed that the 3 dexmedetomidine-ketamine-opioid anesthetic combinations rapidly induced a stage of anesthesia that allowed endotracheal intubation to be accomplished in all dogs, except for 1 dog in the DKH group. The rapid onset of sedation followed by lateral recumbency after injection of these dexmedetomidine-ketamine-opioid anesthetic combinations was similar to that reported for dogs receiving medetomidine-ketamine-butorphanol and medetomidine-ketamine-morphine combinations and confirmed the hypothesis that a single IM injection with a dexmedetomidine-ketamine-opioid combination rapidly induces anesthesia.

Only 1 dog in the DKH group could not be intubated after anesthetic injection and required isoflurane administered via a face mask for induction and endotracheal intubation. There were several possible explanations for the insufficient anesthesia. One probable reason was that the IM injection inadvertently deposited the drugs between the muscle sheaths, which resulted in inadequate or delayed absorption. A second possible reason was that a high amount of excitement in the dog adversely affected the quality of dexmedetomidine-induced sedation via the α2-adrenergic system. A precaution in the packaging insert of dexmedetomidine indicates that nervous or excited animals with high amounts of endogenous catecholamines may have a reduced pharmacological response to α2-adrenoceptor agonists, which results in slow onset of sedative or analgesic actions or diminished depth and duration of sedative effects.

It is interesting that 4 of 8 dogs could not be orotracheally intubated in another study in which investigators used medetomidine (20 µg/kg) and ketamine (5 mg/kg [2.27 mg/lb]) with morphine (0.2 mg/kg). This differs drastically from the results of the study reported here, in which 29 of 30 dogs were intubated easily. The higher dose of the α2-adrenoceptor agonist (dexmedetomidine) used in the present study may have contributed to the higher success rate for endotracheal intubation, compared with the success rate for endotracheal intubation in the study that involved the use of medetomidine-ketamine-morphine. Dexmedetomidine is twice as potent as medetomidine. When the 2 anesthetic protocols were compared, the dose of dexmedetomidine used was equal to 30 µg of medetomidine/kg (13.64 µg of medetomidine/lb), which was 10 µg/kg (4.55 µg/lb) higher than in the other study. In addition, a lower dose of ketamine (3 mg/kg instead of 5 mg/kg) was intentionally used to speed recovery and minimize the potential dissociative carryover effects when dexmedetomidine was reversed with atipamezole. Therefore, the higher dose of dexmedetomidine and lower dose of ketamine likely resulted in successful anesthetic induction and recovery in the present study. Medetomidine contains levomedetomidine, whereas dexmedetomidine does not. It is unknown whether levomedetomidine’s lack of involvement in the present study or its important role in the other medetomidine-ketamine-morphine study influenced the quality of anesthesia and recovery, but the issue warrants further investigation.

In addition, the dose of buprenorphine (40 µg/kg) in combination with dexmedetomidine and ketamine in the present study allowed rapid induction and endotracheal intubation in the DKBup dogs. The buprenorphine dosage used was higher than clinical doses of 10 to 20 µg/kg. This adjustment was based on a report that administration of buprenorphine at a dosage of 15 µg/kg in combination with dexmedetomidine at a dosage of 20 µg/kg failed to induce satisfactory sedation in dogs for radiography of the hip joints. In that study, an additional dose of buprenorphine (3 µg/kg) was administered 20 minutes after the initial IM injection, but the sedation and muscle relaxation were still too poor to allow appropriate positioning of the hip joints for radiography. On the basis of that report, buprenorphine was adjusted to a higher dosage and ketamine was added to the combination to provide anesthesia in dogs for castration in the study reported here. These adjustments resulted in a rapid induction of anesthesia with a depth of anesthesia that allowed endotracheal intubation. The dogs were easily positioned in dorsal recumbency for surgery and would likely have allowed appropriate positioning for radiography of the hip joints. Therefore, buprenorphine at a dosage of 40 µg/kg is recommended when administered in combination with ketamine and dexmedetomidine.

Although the dexmedetomidine-ketamine-opioid combinations rapidly induced anesthesia, a portion of the dogs in each group required supplemental administration of isoflurane to enable the surgeon to complete the castration procedure. Among the treatment groups, the DKBup group had the fewest dogs (1/10) that required supplemental administration of isoflurane. In contrast, there were 3 of 10 and 4 of 10 dogs that required supplemental administration of isoflurane to enable completion of surgery in the DKBut and DKH groups, respectively. This was unexpected because butorphanol and hydromorphone were expected to provide adequate analgesia for a surgical procedure such as castration. This higher frequency of inadequate anesthesia was partially explained by the shorter duration of action for butorphanol and hydromorphone. The surgical procedure was performed approximately 20 to 25 minutes after the initial injection. Although the duration of analgesia for butorphanol and hydromorphone is considered > 20 to 25 minutes in dogs, these opioids were unable to provide consistent analgesia that would allow surgical stimulation in all dogs. However, the low concentration and short duration for supplemental administration of isoflurane suggest that there was some analgesia from the opioids, but just not enough to allow active surgical stimulation such as retracting the spermatic cord of the testes. Once the active surgical procedure was completed, these dogs did not require additional supplemental iso-
flurane. In contrast, the longer duration of analgesia for buprenorphine in combination with injection of dexmedetomidine and ketamine maintained a more consistent surgical plane of anesthesia in the DKBup-treated dogs. It is possible that higher doses of hydromorphone or butorphanol may have yielded results similar to those for the DKBup group, and the use of higher doses of hydromorphone and butorphanol with dexmedetomidine and ketamine during surgery requires investigation. Until such studies are completed, the combination for the DKBup group at the dosages used in the study reported here is recommended for invasive procedures, such as castration in dogs.

In this study, there was a significant decrease in heart rate in all dexmedetomidine-ketamine-opioid groups. The initial bradycardic response was likely attributable to a reflex response to the vasoconstriction induced by dexmedetomidine because blood pressures were high initially. The bradycardia detected during recovery from anesthesia was likely attributable to a reduction in sympathetic outflow as well as a lack of active surgical stimulation. This was indicated by a further reduction during recovery from anesthesia, compared with baseline values, for heart rate (64% to 75% lower than baseline values) and blood pressures (mean arterial blood pressure was 2% to 35% lower than the baseline values), which was accompanied by more frequent and pronounced sinus arrhythmias.

Hypoxemia was detected in all treatment groups during the first 15 minutes after injection of the anesthetic combinations. The hypoxic dogs responded well to supplemental administration of 100% oxygen. The hypoxic response was likely a result of a combination of reduction in respiratory rate, tidal volume, and functional residual capacity in these dogs. The increase in PETCO₂ indicates that there was respiratory depression. Muscle relaxation induced by the anesthetics, combined with positioning in dorsal recumbency for castration, likely caused the reduced functional residual capacity. Because 6 of 10 dogs in the DKBup group and 5 of 10 dogs in each of the DKBup and DKF Groups became hypoxic, it should be mandatory to provide supplemental oxygen when these anesthetic combinations are used.

Atipamezole promptly reversed dexmedetomidine and significantly shortened the recovery time in all 3 treatment groups, compared with that for dogs injected with saline solution. In addition, no carryover effects of ketamine or difficult recoveries were observed in the atipamezole-treated dogs, which supported the use of a low dose of ketamine to facilitate a complete recovery with atipamezole reversal. All the dogs received carprofen prior to the completion of anesthesia and allow endotracheal intubation. However, difficult recoveries were observed in the atipamezole-treated dogs (64% to 75% lower than baseline values), which was accompanied by more frequent and pronounced sinus arrhythmias. Recovery from anesthesia and allow endotracheal intubation. However, difficult recoveries were observed in the atipamezole-treated dogs (64% to 75% lower than baseline values), which was accompanied by more frequent and pronounced sinus arrhythmias.

We concluded that all 3 opioids were suitable for use with dexmedetomidine and ketamine to induce anesthesia and allow endotracheal intubation. However, the DKBup combination was more suitable for invasive or pain-inducing procedures when used at the dosages evaluated in the present study. Hypoxemia developed in all 3 treatment groups, and administration of 100% oxygen was necessary. Bradycardia was common in all anesthetic combinations; however, blood pressures were well maintained. Administration of atipamezole for reversal shortened the recovery from anesthesia without inducing adverse effects and should be viewed as a vital option to facilitate recovery. Therefore, DKBup is recommended as an injectable anesthetic combination (with reversal via administration of atipamezole) for castration of dogs, especially in high-volume settings. Administration of supplemental oxygen is necessary to prevent hypoxemia when any of these anesthetic combinations are used.

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