Evaluation of the Feasibility, Reversibility and Cardiorespiratory Effects of Epidural Dexmedetomidine in Sedated Dogs Undergoing Orchiectomy

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Abstract
The objective of the present study was to evaluate whether epidural dexmedetomidine (DEX) produces sufficient anti-nociception with reversible sedation and cardiorespiratory changes in sedated dogs undergoing orchiectomy. Twelve male dogs weighing 21.7±5.2 kg were used. Dogs received acepromazine (0.025 mg/kg) and morphine (0.25 mg/kg) intramuscularly and a second dose of morphine (0.125 mg/kg) intravenously (IV). DEX (3 µg/kg) was administered epidurally to all dogs (n=12). After confirming complete sensory blockade of the prescrotal region, orchiectomy was performed. If any discomfort was detected during surgery, 2-3 mL lidocaine 1% (maximum two times) was applied into the painful area. Sixty minutes after epidural application, dogs were randomly assigned to receive either treatment of atipamezole (ATP; n=6) or saline (SAL; n=6) IV. None of the dogs required general anesthesia; however, nine out of twelve dogs received lidocaine. The duration of sensory blockade was significantly shorter in ATP than that of SAL. Heart rate, respiratory rate, and rectal temperature showed significantly lower values compared with base after administration of DEX. Administration of atipamezole reversed sedation, sensory blockade and cardiorespiratory changes. In conclusion, epidural DEX did not produce adequate anti-nociception during orchiectomy in sedated dogs. Sedation, sensory blockade and cardiorespiratory changes induced by epidural DEX can be reversed by IV administration of atipamezole.

Keywords: Atipamezole, Dexmedetomidin, Epidural anesthesia, Orchiectomy

INTRODUCTION
Orchiectomy, a common procedure performed in domestic species, is considered a painful surgery in veterinary practice [1]. This surgery is performed under general and/or local anesthesia, with local anesthesia being more common in large animals [2-4]. Using local anesthesia would reduce both the costs and complications associated with general...
anesthesia and provide adequate intra- and postoperative analgesia. Recently, there have been some interests in performing various procedures, from minimally invasive surgeries such as orchietomies to more complicated procedures such as orthopedic operations, by or in combination with local anesthesia in small animals [5-7].

Epidural anesthesia can be employed in a variety of painful conditions to provide anesthesia and analgesia in procedures involving the pelvis, tail, perineum, pelvic limb, and abdomen [8]. Epidural anesthesia could potentially be used alone to provide anesthesia for some surgeries including orthopedic operations and cesarean sections; however, deep sedation is recommended in these situations [9]. Epidural anesthesia could be achieved using different agents and combinations such as local anesthetics, opioids, and/or α2-agonists [10,16].

 Dexmedetomidine (DEX), the active enantiomer of the racemic mixture medetomidine, is the newest available α2-agonist in small and is considered to be at least two times as potent as medetomidine in dogs [11]. Dexmedetomidine is used as a sedative and analgesic in small animals [12]. When used as a premedication in dogs, intravenous administration and/or infusion of DEX decreased propofol and inhalation anesthetic requirement in a dose-dependent manner [13-16]. Epidural administration of DEX in isoflurane-anesthetized dogs has also had a dose-related MAC-sparing effect [17]. The ability to antagonize α2-agonists has made this class of pharmacological agents an appropriate choice in veterinary medicine. Among α2-adrenergic receptor antagonists, atipamezole is used more frequently in small animal practice. Although atipamezole has been employed for reversing changes induced by epidural xylazine [18,19], its effects on epidurally applied DEX have not yet been evaluated.

The first objective of the present study was to evaluate the feasibility and cardiorespiratory effects of using epidural administration of DEX to perform orchietomy in sedated dogs. The second objective was to assess the effects of intravenous (IV) administration of atipamezole on sedation, sensory blockade and cardiorespiratory variables after epidural application of DEX. We hypothesized that epidural administration of DEX would provide sufficient antinociception during orchietomy in sedated dogs. Moreover, intravenous atipamezole would reverse sedation, sensory blockade and cardiorespiratory changes produced by epidural application of DEX.

**MATERIAL and METHODS**

**Animals**

Twelve adult male mongrel dogs weighing 21.7±5.2 kg and aged 1.5-2.5 years old were used in a randomized design. The animals were transferred to the Veterinary Hospital at least two weeks before the study and maintained under the same conditions in individual cages. Food and water were provided twice per day and ad libitum, respectively. Health status was established by a thorough physical examination, complete blood count and total protein. The animals were fasted overnight, but had free access to water until two h prior to the beginning of the procedures. All experiments were started in the morning (09:00-10:00 AM) and finished by 02:00 PM. The Animal Care and Research Committee of Shahid Chamran University of Ahvaz, Ahvaz, Iran, approved all the procedures in the current study [95/3/24/92777].

**Study Design**

Animals received acepromazine (ACE; 0.025 mg/kg; Alfasan, Woerden, Holland) and morphine (MOR; 0.25 mg/kg; Darou Pakhsh, Iran) into the bulk of hamstring muscles. Thirty min later, a 20 G catheter was placed into the left cephalic vein connected to NaCl 0.9% infusion at a rate of 10 mL/kg/h. After injection of one mL lidocaine 1% (Aburaihan Pharma Co., Iran) subcutaneously, a 20 G catheter was also placed into the right dorsal pedal artery. Forty min after administration of sedatives, a half of the first dose of MOR (0.125 mg/kg) was administered IV, and the animals were positioned onto an operating table in sternal recumbency with legs stretched forward. The lumbosacral area was identified, clipped and prepared aseptically. A 22 G 3.8 cm hypodermic needle with the bevel directed cranially was advanced toward the lumbosacral epidural space until it encountered the floor of the canal. Then, the needle was slightly withdrawn 1-2 mm. The correct positioning of the needle was confirmed by a positive hanging drop test. DEX (Hospira, Inc., USA) was administered epidurally at the dose of 3 µg/kg, over about one min (n=12). The Caution was taken to avoid displacement of the needle as evaluated by the lack of resistance against injection. The final volume of the administered drug was set at 0.22 mL/kg using saline. To provide uniform distribution of the drugs, dogs were maintained in sternal recumbency for at least 10 min. All epidural injections were performed by one investigator (H.I.R).

By ensuring sufficient sensory blockade of the prescrotal area, dogs were positioned in right lateral recumbency. The surgery area was clipped and prepared aseptically. Orchietomy was performed via the prescrotal technique with a single skin incision. All procedures were performed by a veterinary surgery resident who was not aware of the treatments. Dogs that were not sedated adequately at the beginning of the orchietomy were excluded from the study. When animals showed any pain-related signs during orchietomy including any discomfort, grunting and changes in cardiorespiratory parameters, 2-3 mL of lidocaine 1% was splash or injected into the painful area including the prescrotal skin, subcutaneous tissues, and spermatic cord, and after about 5 min, surgery was continued. If the animals showed pain again, the second
was removed, a 0.5 mL test sample was collected into a heparinized syringe, and then the first removed sample with 0.5 mL heparinized saline was flushed into the catheter. Using a calibrated gas analyzer (Edan i15, Edan instrument Inc., China), pH, partial arterial pressure of oxygen (PaO₂), partial arterial pressure of carbon dioxide (PaCO₂), bicarbonate ion concentration (HCO₃⁻) and base excess (BE) of collected samples were measured. All data were measured and/or recorded by one investigator.

**Statistical Analysis**

Statistical analysis was undertaken by SPSS version 22 (IBM Corporation, NY, USA) for Windows. Sedation scores were compared using the Mann-Whitney U-test. Comparison of body weights, times to onset of sensory blockade and duration of sensory blockade of the scrotal region after administration of treatments, duration of surgical procedure, HR, f₀, RT, MAP, and blood gas parameters, between two treatments, were performed by Independent-Samples t-test. For comparison of HR, f₀, RT, MAP, and blood gas parameters over time in each group, analysis of variance (ANOVA) for repeated measures and Duncan’s test were employed. P<0.05 was considered as significant level.

**RESULTS**

Body weights were not significantly different between the two treatments: 21.5±4.5 for ATP, vs. 21.9±5.8 for SAL. One dog did not show sufficient sedation and therefore was excluded from the study and was replaced. Sedation was assessed as adequate to perform surgery in the other dogs. No difficulty was encountered in locating the epidural site and injection the drugs. Two dogs did not show complete sensory blockade after 30 min of epidural administration of DEX. The procedure was discontinued and the experiment was repeated for these dogs one week later. The remaining dogs tolerated the surgical procedure without any complications and all recovered uneventfully.

None of the dogs needed general anesthesia to perform or complete the surgical procedure; however, only three out of twelve dogs tolerated orchiectomy without any pain-related responses. Six out of twelve dogs received the first 3 mL of 1% lidocaine; and, three out of twelve dogs required the second 3 mL of 1% lidocaine. Lidocaine was administered in four dogs in the prescrotal skin, two dogs in the subcutaneous tissue plus spermatic cord, and three dogs in the spermatic cord.

Sedation score at the completion of the experiment was significantly lower in ATP than those of SAL at 30 min after administration of ACE-MOR and at the end of the surgery (P<0.01). The time to onset and duration of sensory blockade of the scrotal region and duration of surgery are showed in Table 1. The duration of sensory blockade of the scrotal region after IV administration of treatments was significantly shorter in ATP than that of SAL (P<0.01).

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Evaluation of the Feasibility, Reversibility and ... data related to HR, MAP, f_R, RT and blood gas parameters are summarized in Table 2. HR decreased significantly after epidural administration when compared with the base (P<0.05); however, it returned to base value after atipamezole administration but not after saline administration. While HR progressively increased after atipamezole administration, it remained relatively stable at lower values compared with the base in the saline group. Comparison of HR between the two treatments showed significantly higher values after atipamezole administration than those of saline (P<0.05). MAP was relatively stable during experiment and a significant difference was not detected after either DEX or treatment administration (P>0.05). Sinus arrhythmia and sinus bradycardia (five dogs in each group) with or without second-degree atrioventricular (AV) block, sinoatrial (SA) block and/or sinus arrests were observed after administration of DEX. After treatment, the aforementioned dysrhythmias were occasionally detected in both groups.

Respiratory rate decreased significantly after ACE-MOR administration and this decrease remained throughout the evaluation period (P<0.05). Respiratory rate after atipamezole administration was significantly higher than that of saline at several time points (P<0.05). A slight decrease in RT was observed over time when compared with the base values. Regardless of treatment, this decrease was significant throughout the evaluation period when compared with base (P<0.05). Although it was not significant, RT was relatively higher after treatments in ATP than SAL.

No significant change was detected in pH over time (P>0.05). Hypoxemia (defined as PO_2<95 mmHg) was observed at the sedation time point, which was resolved by oxygen supplementation after epidural administration. After interruption of oxygenation at treatment administration, hypoxemia was not detected and values were within the normal range. Compared with other time points, significantly lower values of PCO_2 were observed at the sedation time point (P<0.05). No significant changes in HCO_3 and BE were observed over time (P>0.05). There were no significant differences concerning blood gas values between treatments (P>0.05).

### Table 1. Sedation scores, time to onset and duration of sensory blockade of scrotal region, and duration of surgery in dogs received epidural DEX (n=12) and intravenous atipamezole (ATP; n=6) or saline (SAL; n=6) undergoing orchiectomy

<table>
<thead>
<tr>
<th>Variable</th>
<th>ATP</th>
<th>SAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation 1 (30 min after administration ACE-MOR)</td>
<td>2 (1-2)</td>
<td>2 (2-4)</td>
</tr>
<tr>
<td>Sedation 2 (at the end of the surgery)</td>
<td>0 (0-1) *,δ</td>
<td>2 (1-2)</td>
</tr>
<tr>
<td>Time to onset of sensory blockade (min)</td>
<td>15±7±6.0</td>
<td></td>
</tr>
<tr>
<td>Duration of sensory blockade (min)</td>
<td>67±7.2 *</td>
<td>89.3±11.0</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>27.9±4.0</td>
<td></td>
</tr>
</tbody>
</table>

* Significantly different between treatments (P<0.05), δ significantly different from Sedation 1 and Sedation 2

### Table 2. Heart rate (HR), mean arterial blood pressure (MAP), respiratory rate (f_R), rectal temperature (RT) and blood gas parameters (mean ± SD) in dogs received epidural dexmedetomidine (n=12) and intravenous atipamezole (ATP; n=6) or saline (SAL; n=6) undergoing orchiectomy. BE: base excess

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base</th>
<th>Sedation</th>
<th>5 min</th>
<th>10 min</th>
<th>20 min</th>
<th>40 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>60±9</td>
<td>61±14 †</td>
<td>38±5 †</td>
<td>36±4 †</td>
<td>33±5 †</td>
<td>40±9 †</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>78±10</td>
<td>80±9</td>
<td>75±9</td>
<td>69±6</td>
<td>90±11</td>
<td>87±12</td>
</tr>
<tr>
<td>f_R (breaths/min)</td>
<td>28±9</td>
<td>17±3 †</td>
<td>12±3 †</td>
<td>12±4 †</td>
<td>13±3 †</td>
<td>12±3 †</td>
</tr>
<tr>
<td>RT (°C)</td>
<td>38.8±0.3</td>
<td>38.4±0.3 †</td>
<td>38.1±0.3 †</td>
<td>38.1±0.2 †</td>
<td>38.0±0.3 †</td>
<td>37.8±0.5 †</td>
</tr>
<tr>
<td>PH</td>
<td>ND</td>
<td>7.35±0.01</td>
<td>7.33±0.01</td>
<td>7.34±0.01</td>
<td>7.33±0.02</td>
<td></td>
</tr>
<tr>
<td>PO_2 (mmHg)</td>
<td>ND</td>
<td>90±6</td>
<td>447±66 †</td>
<td>446±87 †</td>
<td>424±68 †</td>
<td></td>
</tr>
<tr>
<td>PCO_2 (mmHg)</td>
<td>ND</td>
<td>31±4</td>
<td>40±3 †</td>
<td>39±6 †</td>
<td>38±6 †</td>
<td></td>
</tr>
<tr>
<td>HCO_3 (mEq/L)</td>
<td>ND</td>
<td>17±2</td>
<td>20±3</td>
<td>21±4</td>
<td>19±2</td>
<td></td>
</tr>
<tr>
<td>BE</td>
<td>ND</td>
<td>-8±3</td>
<td>-5±3</td>
<td>-5±4</td>
<td>-7±3</td>
<td></td>
</tr>
</tbody>
</table>

ND: not determined, † Significantly different from base (P<0.05), δ Significantly different from base in SAL group (P<0.05), ‡ Significantly different from Sedation (P<0.05), * Significantly different between treatments (P<0.05)
DISCUSSION

The results of the present study demonstrated that epidural administration of DEX at the dose of 3 µg/kg did not provide sufficient anti-nociception during orchiectomy in sedated dogs. Sedation produced by ACE and MOR increased to moderate to deep levels after DEX application. Epidural DEX decreased HR over time and had no significant effect on MAP. Both $f_t$ and RT showed lower values after epidural administration of DEX compared to those of base. Administration of atipamezole intravenously (0.03 mg/kg), in comparison to saline, decreased the sedation level, reduced the duration of sensory blockade, increased HR, and had no significant effect on MAP. Respiratory rate was higher at several time points, and RT showed nonsignificant higher values after atipamezole administration when compared with saline. Blood gas changes were not clinically significant in the current study.

Epidural application of $\alpha_2$-adrenergic agonists such as DEX is of interest as $\alpha_2$-adrenergic receptors have been identified in the spinal cord and showed to have presynaptic and postsynaptic actions on the modulation of pain [20,21]. These effects appear to be different from the vasoconstrictive action of such drugs [9]. Furthermore, epidural administration of low doses (3.3 µg/kg) of DEX in comparison to IV administration of relatively high doses (10 µg/kg) has been shown that potentiates and prolongs the analgesic properties of DEX in dogs (240 min analgesia compared with 90 min) [22]. Therefore, epidural application of DEX might be associated with lower occurrence and less severe adverse effects including bradycardia and reduction in cardiac output than what would be observed after IV administration [11,22]. The reversibility of $\alpha_2$-adrenergic agonists is another factor that makes these pharmacologic agents as an appropriate choice in clinical use since this feature could potentially reduce hospitalization and the risks associated with administration of high doses.

In the current study, epidural administration of DEX was employed to provide anti-nociception during orchiectomy in dogs. Although, assessment of sensory blockade in the skin of the surgical site with superficial and deep pinprick test and pressure applied by a hemostat elicited no responses, anti-nociception was not sufficient for pain induced by incision and manipulation of testicles and spermatic cords. Pohl et al. [23] have already showed that epidural application of DEX at a dose of 2 µg/kg with lidocaine could not produce sufficient analgesia during ovariohysterectomy in dogs and all of the animals were finally submitted to isoflurane anesthesia. In an earlier study in dogs, 1.5, 3 and 6 µg/kg epidural DEX yielded isoflurane MAC-sparing effect in a dose-dependent manner [17]. Since the authors of the present investigation were not aware of the effective dose of epidural DEX in conscious dogs, 3 µg/kg DEX was used to avoid undesirable cardiovascular consequences. Considering that this dose was sufficient to prevent pain responses at the time of evaluation, a greater dose might increase the likelihood of successful orchietomy under epidural anesthesia with DEX. One of the limitations of the current study is that just one dose rate of DEX was examined.

It is common to observe sedation after epidural administration of $\alpha_2$-agonists as a result of systemic absorption of the drug [9]. Moreover, co-administration of opioids and $\alpha_2$-agonists might produce more profound and longer lasting sedation [24,25]. In the present study, epidural administration of DEX enhanced previously produced sedation; even though, the probable synergetic effects of MOR and DEX need to be investigated by further studies.

Cardiovascular effects of DEX, as with other $\alpha_2$-agonists, involve decreased HR, decreased cardiac output and increased systemic vascular resistance [11,26]. In the studies by Camagnol et al. [17] and Pohl et al. [23], HR decreased after epidural administration of DEX in dogs. Similar to previous studies, in this investigation HR decreased after epidural application of DEX. The decrease in HR after administration of $\alpha_2$-agonists is attributed to increased systemic vascular resistance (in the early phase) and decreased central sympathetic outflow (in the later phase) [20]. Blood pressure, after administration of $\alpha_2$-agonists, has a biphasic manner in which it increases transiently followed by prolonged hypotension [24,27], however, it has been speculated that $\alpha_2$-agonists might not be linked to hypotension in dogs [20]. Indeed, in a number of investigations blood pressure remained in an acceptable range after administration of $\alpha_2$-agonists [11,13,21,28,29], suggesting that the predominant vasoconstriction produced by $\alpha_2$-agonists likely prevents severe hypotension in dogs [20]. In the current study, MAP remained relatively constant after epidural administration of DEX; however, it should be noted that MAP was at or below the limits of the reported normal range all over the evaluation period. This finding might be explained by using of indigenous dogs with lower normal MAP in the present investigation.

A dose-dependent decrease in $f_t$ and minute volume were reported after $\alpha_2$-agonists administration in humans [27]. Significant reduction in $f_t$ in dogs given medetomidine (30 µg/kg, IM) has also been reported by Ko et al. [28]. In contrast, epidural (4 µg/kg) and IM (50, 100 and 150 µg/kg) administration of DEX did not change $f_t$ in cats [30,31]. In the current study, $f_t$ remained at lower values in comparison to base after epidural administration of DEX; nevertheless, blood gas values showed no clinical significance. Similar results have been obtained in dogs with clinically used doses of xylazine in which despite observing a decrease in $f_t$, no changes in pH, PaO₂, and PaCO₂ were recorded. The authors of the latter study have attributed the results to concomitant increase in tidal volume with decrease in respiratory rate that consequently resulted in constant minute ventilation [32]. The same mechanism might have been played a role in the present study. Lower values of PaO₂
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