

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

Hadi IMANI RASTABI <sup>1,a</sup> Hadi NADDAF <sup>1</sup> Bahman MOSALLANEJAD <sup>1</sup> Ahmad KHAJEH <sup>1</sup>

<sup>1</sup> Department of Clinical Sciences, Faculty of Veterinary Medicine, Shahid Chamran University of Ahvaz, Ahvaz, IRAN  
<sup>a</sup> ORCID: 0000-0002-1564-7240

Article ID: KVFD-2019-21943 Received: 30.01.2019 Accepted: 26.06.2019 Published Online: 30.06.2019

## How to Cite This Article

Imani Rastabi H, Naddaf H, Mosallanejad B, Khajeh A: Evaluation of the feasibility, reversibility and cardiorespiratory effects of epidural dexmedetomidine in sedated dogs undergoing orchiectomy. *Kafkas Univ Vet Fak Derg*, 25 (6): 807-813, 2019. DOI: 10.9775/kvfd.2019.21943

## 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, Dexmedetomidine, Epidural anesthesia, Orchiectomy

## Orşiektomi Yapılan Sedasyonlu Köpeklerde Epidural Deksmetomidinin Fizibilite, Reverzibilite ve Kardiyorespiratuvar Etkilerinin Değerlendirilmesi

### Öz

Bu çalışmanın amacı; orşiektomi yapılan sedasyonlu köpeklerde epidural deksmedetomidinin (DEX) geri dönüşlü sedasyon ve kardiyorespiratuvar değişiklikleri ile yeterli anti-nosisepsiyon üretip üretmediğini değerlendirmektir. Çalışmada ortalama ağırlıkları 21.7±5.2 kg olan on iki erkek köpek kullanıldı. Köpeklere intramüsküler yolla asepromazin (0.025 mg/kg) ve morfin (0.25 mg/kg) ardından intravenöz yolla (IV) ikinci bir doz morfin (0.125 mg/kg) uygulandı. Tüm köpeklere (n=12) epidural yolla DEX (3 µg/kg) uygulandı. Prescrotal bölgenin tam duyuşal blokajı sağlandıktan sonra orşiektomi operasyonu yapıldı. Ameliyat sırasında herhangi bir rahatsızlık tespit edilirse, ağırlı bölgeye 2-3 mL %1'lik lidokain (en fazla iki kez) uygulandı. Epidural uygulamadan altmış dakika sonra, köpekler IV atipamezol (ATP; n=6) veya salin (SAL; n=6) tedavisi alacak şekilde rastgele gruplandırıldı. Köpeklerin hiçbirinde genel anestezi uygulanması gerekmedi; ancak, on iki köpekten dokuzuna lidokain uygulandı. ATP'de duyuşal blokajın süresi, SAL'dan daha kısaydı. Kalp atış hızı, solunum hızı ve rektal sıcaklık, DEX uygulamasından sonraki ölçümler ile karşılaştırıldığında önemli ölçüde düşüş gösterdi. Atipamezol uygulaması, sedasyon, duyuşal blokaj ve kardiyorespiratuvar değişiklikleri tersine çevirdi. Sonuç olarak, epidural DEX, sedasyon uygulanan köpeklerde orşiektomi sırasında yeterli anti-nosisepsiyon etki üretmediği belirlendi. Epidural DEX'in neden olduğu sedasyon, duyuşal blokaj ve kardiyorespiratuvar değişiklikler IV atipamezol uygulamasıyla tersine çevrilebilir.

**Anahtar sözcükler:** Atipamezol, Deksmetomidin, Epidural anestezi, Orşiektomi

## INTRODUCTION

Orchiectomy, a common procedure performed in domestic species, is considered a painful surgery in veterinary

practice <sup>[1]</sup>. This surgery is performed under general and/or local anesthesia, with local anesthesia being more common in large animals <sup>[2-4]</sup>. Using local anesthesia would reduce both the costs and complications associated with general



### İletişim (Correspondence)



+98 913 382 3324



h.imani@scu.ac.ir

anesthesia and provide adequate intra- and postoperative analgesia. Recently, there have been some interests in performing various procedures, from minimally invasive surgeries such as orchiectomies 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  $\alpha_2$ -agonists [9,10].

Dexmedetomidine (DEX), the active enantiomer of the racemic mixture medetomidine, is the newest available  $\alpha_2$ -agonist in small animals and it is considered to be at least two times as potent as medetomidine in dogs [11]. Dexmedetomidine is used as a sedative and an 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  $\alpha_2$ -agonists has made this class of pharmacological agents an appropriate choice in veterinary medicine. Among  $\alpha_2$ -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 orchiectomy 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 orchiectomy 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  $21.7 \pm 5.2$  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  $\mu$ g/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. Orchiectomy 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 orchiectomy were excluded from the study. When animals showed any pain-related signs during orchiectomy including any discomfort, grunting and changes in cardiorespiratory parameters, 2-3 mL of lidocaine 1% was splashed 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

2-3 mL of lidocaine 1% was administered in the same manner. If the dogs showed pain-related responses for the third time, propofol (4 mg/kg; B Braun, Melsungen, Germany) and midazolam (0.2 mg/kg; Exir, Pharmaceutical Co., Iran) prepared previously, were administered IV to continue the procedure under general anesthesia. After accomplishing the surgery, animals were positioned in sternal recumbency and maintained in this position until 60 min had elapsed after epidural administration. At this time, and after administration of ketoprofen (2 mg/kg; Razak, Tehran, Iran), animals received either treatment with atipamezole (ATP; 0.03 mg/kg; Laboratorios Syva, Spain; n=6) or saline (SAL; n=6) IV, brought to the total volume of two mL. Animals received 100% oxygen, after epidural administration until the end of the surgery, via a face mask at the rate of 100 mL/kg/min using a non-rebreathing circuit system. Using a blanket over the animals, it was attempted to maintain rectal temperature above 37°C, during the period of after epidural administration through epidural recovery. At the time of treatment administration, oxygen delivery and fluid therapy were interrupted.

#### Assessments and Data Collection

Sedation was qualitatively scored at 30 min after administration of ACE-MOR, at the end of surgery, and at the completion of the experiment for each dog, using a numerical scaling system: 1- mild, 2- moderate, 3- deep, and 4- very deep. The onset and duration of sensory blockade were recorded. Sensory blockade was confirmed when responses to superficial and deep pin prick test using a 25 G needle, and pressure applied by a hemostat closed at the second ratchet for 15 s, was negative. Duration of surgery, from draping until last suture knotting, was also recorded.

Heart rate (HR), non-invasive mean arterial blood pressure (MAP), respiratory rate ( $f_R$ ), and rectal temperature (RT) were measured and recorded at base, at 30 min after administration of ACE-MOR (sedation), and at 5, 10, 20, and 40 min after epidural administration, and 5, 15, 30, and 60 min after treatments administration. HR was counted through hearing by a stethoscope. MAP was measured and recorded by applying an appropriate blood pressure cuff (with the cuff width to metatarsal circumference ratio of at least 40%) over the left dorsal pedal artery, connected to a multi-parameter monitoring system (Burtons, Guardian Industrial Estate, UK).  $f_R$  was measured by observation of chest movements, and RT was recorded through a digital thermometer. Lead II electrocardiogram (ECG) was recorded at 5, 20, and 40 min after epidural administration and 5 and 15 min after treatment administration.

Blood samples were taken anaerobically through the dorsal pedal artery at 30 min after administration of ACE-MOR (sedation), and at 5, 20, and 40 min after epidural administration and at 15 and 30 min after administration of treatment. One mL blood from the arterial catheter 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 (PaO<sub>2</sub>), partial arterial pressure of carbon dioxide (PaCO<sub>2</sub>), bicarbonate ion concentration (HCO<sub>3</sub><sup>-</sup>) 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,  $f_R$ , RT, MAP, and blood gas parameters, between two treatments, were performed by Independent-Samples t-test. For comparison of HR,  $f_R$ , 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 orchietomy 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).

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 orchietomy

Variable	ATP	SAL
Sedation 1 (30 min after administration ACE-MOR)	2 (1-2)	
Sedation 2 (at the end of the surgery)	2 (2-4)	
Sedation 3 (at the completion of the experiment)	0 (0-1) *, $\delta$	2 (1-2)
Time to onset of sensory blockade (min)	15.7 $\pm$ 6.0	
Duration of sensory blockade (min)	67 $\pm$ 7.2 *	89.3 $\pm$ 11.0
Duration of surgery (min)	27.9 $\pm$ 4.0	

\* Significantly different between treatments ( $P<0.05$ ),  $\delta$  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  $\pm$  SD) in dogs received epidural dexmedetomidine ( $n=12$ ) and intravenous atipamezole (ATP;  $n=6$ ) or saline (SAL;  $n=6$ ) undergoing orchietomy. BE: base excess

Variable	Base	Sedation		Epidural					Treatment	Group	5 min	15 min	30 min	60 min
				5 min	10 min	20 min	40 min				ATP	SAL	ATP	SAL
HR (beats/min)	60 $\pm$ 9	61 $\pm$ 14 †		38 $\pm$ 5 †	36 $\pm$ 4 †	33 $\pm$ 5 †	40 $\pm$ 9 †		ATP	48 $\pm$ 14 *	48 $\pm$ 8 *	49 $\pm$ 13 *	59 $\pm$ 15 *	
									SAL	37 $\pm$ 5 †, $\delta$	39 $\pm$ 3 †, $\delta$	38 $\pm$ 3 †, $\delta$	36 $\pm$ 5 †, $\delta$	
MAP (mmHg)	78 $\pm$ 10	80 $\pm$ 9		75 $\pm$ 9	69 $\pm$ 6	90 $\pm$ 11	87 $\pm$ 12		ATP	86 $\pm$ 8	76 $\pm$ 12	85 $\pm$ 12	87 $\pm$ 14	
									SAL	78 $\pm$ 12	84 $\pm$ 11	85 $\pm$ 4	85 $\pm$ 15	
$f_R$ (breaths/min)	28 $\pm$ 9	17 $\pm$ 3 †		12 $\pm$ 3 †	12 $\pm$ 4 †	13 $\pm$ 3 †	12 $\pm$ 3 †		ATP	15 $\pm$ 5 †	17 $\pm$ 4 †,*	16 $\pm$ 6 †,*	15 $\pm$ 1 †	
									SAL	13 $\pm$ 4 †	12 $\pm$ 3 †	11 $\pm$ 5 †	12 $\pm$ 5 †	
RT (°C)	38.8 $\pm$ 0.3	38.4 $\pm$ 0.3 †		38.1 $\pm$ 0.3 †	38.1 $\pm$ 0.2 †	38.0 $\pm$ 0.3 †	37.8 $\pm$ 0.5 †		ATP	37.8 $\pm$ 0.5 †	37.7 $\pm$ 0.7 †	37.9 $\pm$ 0.5 †	37.8 $\pm$ 0.2 †	
									SAL	37.7 $\pm$ 0.1 †	37.5 $\pm$ 0.2 †	37.5 $\pm$ 0.2 †	37.3 $\pm$ 0.2 †	
PH	ND	7.35 $\pm$ 0.01		7.33 $\pm$ 0.01	ND	7.34 $\pm$ 0.01	7.33 $\pm$ 0.02		ATP	ND	7.34 $\pm$ 0.04	7.37 $\pm$ 0.01	ND	
									SAL	ND	7.32 $\pm$ 0.02	7.33 $\pm$ 0.04	ND	
$PO_2$ (mmHg)	ND	90 $\pm$ 6		447 $\pm$ 66 ‡	ND	446 $\pm$ 87 ‡	424 $\pm$ 68 ‡		ATP	ND	96 $\pm$ 3	98 $\pm$ 4	ND	
									SAL	ND	97 $\pm$ 2	97 $\pm$ 5	ND	
$PCO_2$ (mmHg)	ND	31 $\pm$ 4		40 $\pm$ 3 ‡	ND	39 $\pm$ 6 ‡	38 $\pm$ 6 ‡		ATP	ND	33 $\pm$ 7	33 $\pm$ 2	ND	
									SAL	ND	34 $\pm$ 2	35 $\pm$ 3	ND	
$HCO_3^-$ (mEq/L)	ND	17 $\pm$ 2		20 $\pm$ 3	ND	21 $\pm$ 4	19 $\pm$ 2		ATP	ND	20 $\pm$ 3	19 $\pm$ 2	ND	
									SAL	ND	17 $\pm$ 2	17 $\pm$ 1	ND	
BE	ND	-8 $\pm$ 3		-5 $\pm$ 3	ND	-5 $\pm$ 4	-7 $\pm$ 3		ATP	ND	-7 $\pm$ 3	-8 $\pm$ 2	ND	
									SAL	ND	-9 $\pm$ 2	-9 $\pm$ 1	ND	

ND: not determined, † Significantly different from base ( $P<0.05$ ),  $\delta$  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  $\mu\text{g}/\text{kg}$  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  $f_R$  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 non-significant 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<sup>[20,21]</sup>. These effects appear to be different from the vasoconstrictive action of such drugs<sup>[9]</sup>. Furthermore, epidural administration of low doses (3.3  $\mu\text{g}/\text{kg}$ ) of DEX in comparison to IV administration of relatively high doses (10  $\mu\text{g}/\text{kg}$ ) has been showed that potentiates and prolongs the analgesic properties of DEX in dogs (240 min analgesia compared with 90 min)<sup>[22]</sup>. 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<sup>[13,22]</sup>. 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 pin prick 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.<sup>[23]</sup> have already showed that epidural application of DEX at a dose of 2  $\mu\text{g}/\text{kg}$  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  $\mu\text{g}/\text{kg}$  epidural DEX yielded isoflurane MAC-sparing effect in a dose-dependent manner<sup>[17]</sup>. Since the authors of the present investigation were not aware of the effective dose of epidural DEX in conscious dogs, 3  $\mu\text{g}/\text{kg}$  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 orchiectomy 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<sup>[9]</sup>. Moreover, co-administration of opioids and  $\alpha_2$ -agonists might produce more profound and longer lasting sedation<sup>[24,25]</sup>. 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<sup>[13,26]</sup>. In the studies by Camagnol et al.<sup>[17]</sup> and Pohl et al.<sup>[23]</sup>, 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)<sup>[26]</sup>. Blood pressure, after administration of  $\alpha_2$ -agonists, has a biphasic manner in which it increases transiently followed by prolonged hypotension<sup>[26,27]</sup>, however, it has been speculated that  $\alpha_2$ -agonists might not be linked to hypotension in dogs<sup>[26]</sup>. Indeed, in a number of investigations blood pressure remained in an acceptable range after administration of  $\alpha_2$ -agonists<sup>[11,13,23,28,29]</sup>, suggesting that the predominant vasoconstriction produced by  $\alpha_2$ -agonists likely prevents severe hypotension in dogs<sup>[26]</sup>. 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  $f_R$  and minute volume were reported after  $\alpha_2$ -agonists administration in humans<sup>[27]</sup>. Significant reduction in  $f_R$  in dogs given medetomidine (30  $\mu\text{g}/\text{kg}$ , IM) has also been reported by Ko et al.<sup>[28]</sup>. In contrast, epidural (4  $\mu\text{g}/\text{kg}$ ) and IM (50, 100 and 150  $\mu\text{g}/\text{kg}$ ) administration of DEX did not change  $f_R$  in cats<sup>[30,31]</sup>. In the current study,  $f_R$  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  $f_R$ , no changes in pH, PaO<sub>2</sub> and PaCO<sub>2</sub> 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<sup>[32]</sup>. The same mechanism might have been played a role in the present study. Lower values of PaO<sub>2</sub>

at the sedation time point in the current study increased after oxygenation which indicated that supplemental oxygenation could be considered as an important aspect in ACE-MOR sedated dogs that received epidural DEX.

A gradual decrease in RT was observed after sedation and this decrease continued after epidural application of DEX. A slight but progressive decrease in RT was also detected after epidural administration of DEX in cats<sup>[31]</sup>. A decrease in RT was observed in dogs treated with IM DEX; however, this decrease remained on average within clinically acceptable range<sup>[33]</sup>. Hypothermia induced by  $\alpha_2$ -agonists has been attributed to decrease in heat production due to muscle relaxation or because of noradrenergic hypothalamic mechanisms of thermoregulation<sup>[34,35]</sup>. Based on the results of the current study and other investigations, precise monitoring and maintaining the body temperature are recommended in dogs receiving  $\alpha_2$ -agonists.

Intravenous atipamezole was employed to reverse clinical and pharmacologic effects of DEX in dogs. In an earlier study, atipamezole was able to antagonize the sedative and not the analgesic effects of epidural xylazine in dogs<sup>[18]</sup>. In contrast, epidurally and IV administered atipamezole have reversed both sedation and analgesia in cattle that received epidural xylazine<sup>[19]</sup>. In a study in dogs, IM atipamezole has completely reversed sedation and analgesia induced by IM DEX; however, HR and  $f_R$  did not return to presedation values after atipamezole administration<sup>[33]</sup>. In the current study, atipamezole when compared with saline, decreased the duration of sensory blockade, reduced sedation and increased HR and  $f_R$ . Although HR returned to the presedation values in ATP,  $f_R$  did not reach to the base in this group. As with Granholm et al.<sup>[33]</sup>, the inability of atipamezole to reverse changes in  $f_R$  could be attributed to the attenuation of sympathetic nervous system activation and lower concentration of stress-related hormones inducing after  $\alpha_2$ -agonists administration reported by other investigators<sup>[36]</sup>.

In this study, epidural application of DEX did not provide sufficient anti-nociception during orchietomy in sedated dogs at the dose rate tested. Epidural DEX produced a degree of sedation in dogs and induced some changes in cardiorespiratory parameters. Intravenous administration of atipamezole decreased the sedation level, reduced the duration of sensory blockade and reversed cardiorespiratory changes.

## REFERENCES

- Lorena SE, Luna SP, Lascalles BDX, Corrente JE:** Current attitudes regarding the use of perioperative analgesics in dogs and cats by Brazilian veterinarians. *Vet Anaesth Analg*, 41 (1): 82-89, 2014. DOI: 10.1111/vaa.12104
- Nickell J, Barter LS, Dechant JE:** Effects of intratesticular and incisional local anesthetic administration for castration of alpacas anesthetized with intramuscular ketamine-xylazine-butorphanol. *Vet Surg*, 44 (2): 168-173, 2015. DOI: 10.1111/j.1532-950X.2014.12285.x
- Park SJ, Piao M, Kim H, Kang HJ, Seo J, Lee S, Baik M:** Effects of castration and a lidocaine-plus-flunixin treatment on growth and indicators of pain, inflammation, and liver function in Korean cattle bull calves. *Livest Sci*, 216, 61-66, 2018. DOI: 10.1016/j.livsci.2018.07.010
- Racine J, Vidondo B, Ramseyer A, Koch C:** Complications associated with closed castration using the Henderson equine castration instrument in 300 standing equids. *Vet Surg*, 48 (1): 21-28, 2019. DOI: 10.1111/vsu.12960
- Campoy L, Martin-Flores M, Ludders JW, Gleed RD:** Procedural sedation combined with locoregional anesthesia for orthopedic surgery of the pelvic limb in 10 dogs: Case series. *Vet Anaesth Analg*, 39 (4): 436-440, 2012. DOI: 10.1111/j.1467-2995.2012.00712.x
- Kushnir Y, Toledano N, Cohen L, Bdolah-Abram T, Shilo-Benjamini Y:** Intratesticular and incisional line infiltration with ropivacaine for castration in medetomidine-butorphanol-midazolam sedated dogs. *Vet Anaesth Analg*, 44 (2): 346-355, 2017. DOI: 10.1016/j.vaa.2016.03.007
- Yayla S, Kaçar C, Kılıç E, Kaya S, Kuru M, Ermutlu ÇŞ, Özyayın İ, Hüseyinoğlu Ü, Ögün M:** The effects of intrathecal administration of bupivacaine or ropivacaine following administration of propofol in dogs undergoing ovariohysterectomy. *Kafkas Univ Vet Fak Derg*, 23 (3): 363-367, 2017. DOI: 10.9775/kvfd.2016.16665
- Campoy L, Read M, Peralta S:** Canine and Feline Local Anesthetic and Analgesic Techniques. In, Grimm KA, Lamont LA, Tranquilli WJ, Greene SA, Robertson SA (Eds): *Veterinary Anesthesia and Analgesia, The Fifth Edition of Lumb and Jones.*, 827-856, John Wiley & Sons, Pondicherry, India, 2015.
- Jones RS:** Epidural analgesia in the dog and cat. *Vet J*, 161 (2): 123-131, 2001. DOI: 10.1053/tvj.2000.0528
- Steagall PVM, Simon BT, Teixeira Neto FJ, Luna SPL:** An update on drugs used for lumbosacral epidural anesthesia and analgesia in dogs. *Front Vet Sci*, 4:68, 2017. DOI: 10.3389/fvets.2017.00068
- Kuusela E, Raekallio M, Anttila M, Falck I, Molsa S, Vainio O:** Clinical effects and pharmacokinetics of medetomidine and its enantiomers in dogs. *J Vet Pharmacol Ther*, 23 (1): 15-20, 2000. DOI: 10.1046/j.1365-2885.2000.00245.x
- Bennett RC, Restitutti F:** Dexmedetomidine or medetomidine: Which should veterinary surgeons select? *Companion Anim*, 21 (3): 128-137, 2016. DOI: 10.12968/coan.2016.21.3.128
- Bloor BC, Frankland M, Alper G, Raybould D, Weitz J, Shurtliff M:** Hemodynamic and sedative effects of dexmedetomidine in dog. *J Pharmacol Exp Ther*, 263 (2): 690-697, 1992.
- Pascoe PJ, Raekallio M, Kuusela E, McKusick B, Granholm M:** Changes in the minimum alveolar concentration of isoflurane and some cardiopulmonary measurements during three continuous infusion rates of dexmedetomidine in dogs. *Vet Anaesth Analg*, 33 (2): 97-103, 2006. DOI: 10.1111/j.1467-2995.2005.00236.x
- Smith CK, Seddighi R, Cox SK, Sun X, Knych HK, Doherty TJ:** Effect of dexmedetomidine on the minimum infusion rate of propofol preventing movement in dogs. *Vet Anaesth Analg*, 44 (6): 1287-1295, 2017. DOI: 10.1016/j.vaa.2017.07.004
- Vasiljević M, Krstić V, Stanković S, Zrimšek P, Svete AN, Seliškar A:** Cardiac troponin I in dogs anaesthetized with propofol and sevoflurane: The Influence of medetomidine premedication and inspired oxygen fraction. *Vet Anaesth Analg*, 45 (6): 745-753, 2018. DOI: 10.1016/j.vaa.2018.07.003
- Campagnol D, Neto FJT, Giordano T, Ferreira TH, Monteiro ER:** Effects of epidural administration of dexmedetomidine on the minimum alveolar concentration of isoflurane in dogs. *Am J Vet Res*, 68 (12): 1308-1318, 2007. DOI: 10.2460/ajvr.68.12.1308
- Rector E, Kramer S, Kietzmann M, Hart S, Nolte I:** Evaluation of the antinociceptive effect of systemic and epidurally applied xylazine in general anesthesia with isoflurane in dogs and the effect of atipamezole infection on postoperative analgesia. *Berl Munch Tierarztl Wochenschr*, 111 (11-12): 438-451, 1998.
- Lee I, Yamagishi N, Oboshi K, Yamada H:** Antagonistic effects of intravenous or epidural atipamezole on xylazine-induced dorsolumbar epidural analgesia in cattle. *Vet J*, 166 (2): 194-197, 2003. DOI: 10.1016/S1090-0233(03)00026-1

- 20. Sullivan AF, Kalso EA, McQuay HJ, Dickenson AH:** The antinociceptive actions of dexmedetomidine on dorsal horn neuronal responses in the anaesthetized rat. *Eur J Pharmacol*, 215 (1): 127-133, 1992. DOI: 10.1016/0014-2999(92)90617-D
- 21. Sullivan AF, Dashwood MR, Dickenson AH:**  $\alpha_2$ -adrenoceptor modulation of nociception in rat spinal cord: Location, effects and interactions with morphine. *Eur J Pharmacol*, 138 (2): 169-177, 1987. DOI: 10.1016/0014-2999(87)90430-4
- 22. Sabbe MB, Penning JP, Ozaki GT, Yaksh TL:** Spinal and systemic action of the alpha 2 receptor agonist dexmedetomidine in dogs. Antinociception and carbon dioxide response. *Anesthesiology*, 80 (5): 1057-1072, 1994.
- 23. Pohl VH, Carregaro AB, Lopes C, Gehrcke MI, Muller D, Garlet CD:** Epidural anesthesia and postoperative analgesia with alpha-2 adrenergic agonists and lidocaine for ovariohysterectomy in bitches. *Can J Vet Res*, 76 (3): 215-220, 2012.
- 24. Nishimura LT, Auckburally A, Santilli J, Vieira BHB, Garcia DO, Honsho CS, de Mattos-Junior E:** Effects of dexmedetomidine combined with commonly administered opioids on clinical variables in dogs. *Am J Vet Res*, 79 (3): 267-275, 2018. DOI: 10.2460/ajvr.79.3.267
- 25. Raillard M, Michaut-Castrillo J, Spreux D, Gauthier O, Touzot-Jourde G, Holopherne-Doran D:** Comparison of medetomidine-morphine and medetomidine-methadone for sedation, isoflurane requirement and postoperative analgesia in dogs undergoing laparoscopy. *Vet Anaesth Analg*, 44 (1): 17-27, 2017. DOI: 10.1111/vaa.12394
- 26. Murrell JC, Hellebrekers LJ:** Medetomidine and dexmedetomidine: A review of cardiovascular effects and antinociceptive properties in the dog. *Vet Anaesth Analg*, 32 (3): 117-127, 2005. DOI: 10.1111/j.1467-2995.2005.00233.x
- 27. Maze M, Tranquilli W:** Alpha-2 adrenoceptor agonists: Defining the role in clinical anesthesia. *Anesthesiology*, 74, 581-605, 1991.
- 28. Ko JCH, Fox SM, Mandsager RE:** Sedative and cardiorespiratory effects of medetomidine, medetomidine-butorphanol, and medetomidine-ketamine in dogs. *J Am Vet Med Assoc*, 216 (10): 1578-1583, 2000. DOI: 10.2460/javma.2000.216.1578
- 29. Kuusela E, Vainio O, Short CE, Leppäluoto J, Huttunen P, Ström S, Huju V, Valtonen A, Raekallio M:** A comparison of propofol infusion and propofol/isoflurane anaesthesia in dexmedetomidine premedicated dogs. *J Vet Pharmacol Ther*, 26 (3): 199-204, 2003. DOI: 10.1046/j.1365-2885.2003.00465.x
- 30. Ansah O, Raekallio M, Vainio O:** Comparison of three doses of dexmedetomidine with medetomidine in cats following intramuscular administration. *J Vet Pharmacol Ther*, 21, 380-387, 1998. DOI: 10.1046/j.1365-2885.1998.00155.x
- 31. Souza SS, Intelisano TR, De Biaggi CP, Moura CA, Selmi AL, Dias RA, Cortopassi SRG:** Cardiopulmonary and isoflurane-sparing effects of epidural or intravenous infusion of dexmedetomidine in cats undergoing surgery with epidural lidocaine. *Vet Anaesth Analg*, 37 (2): 106-115, 2010. DOI: 10.1111/j.1467-2995.2009.00512.x
- 32. Haskins SC, Patz JD, Farver TB:** Xylazine and xylazine-ketamine in dogs. *Am J Vet Res*, 47 (3): 636-641, 1986.
- 33. Granholm M, McKusick BC, Westerholm FC, Aspegren JC:** Evaluation of the clinical efficacy and safety of dexmedetomidine or medetomidine in cats and their reversal with atipamezole. *Vet Anaesth Analg*, 33 (4): 214-223, 2006. DOI: 10.1111/j.1467-2995.2005.00259.x
- 34. Pypendop BH, Verstegen JP:** Cardiovascular effects of romifidine in dogs. *Am J Vet Res*, 62 (4): 490-495, 2001. DOI: 10.2460/ajvr.2001.62.490
- 35. Virtanen R:** Pharmacological profiles of medetomidine and its antagonist, atipamezole. *Acta Vet Scand Suppl*, 85, 29-37, 1989.
- 36. Väisänen M, Raekallio M, Kuusela E, Huttunen P, Leppäluoto J, Kirves P, Vainio O:** Evaluation of the perioperative stress response in dogs administered medetomidine or acepromazine as part of the preanesthetic medication. *Am J Vet Res*, 63 (7): 969-975, 2002. DOI: 10.2460/ajvr.2002.63.969