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Evaluation of the Anesthetic Properties of Dexmedetomidine and Dexmedetomidine-Ketamine Combination and the Properties of Atipamezole as a Reversal Agent in Domestic Pigeons*

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Abstract: The aim of this study was to determine the anesthetic efficacy of dexmedetomidine and ketamine alone and dexmedetomidine-ketamine combination and the effects of α2 adrenergic reversal atipamezole in domestic pigeons (Columba livia). In DX group, dexmedetomidine (80 µg/kg), in K group, ketamine (100 mg/kg) alone, in DXK group, dexmedetomidine (40 µg/kg) and ketamine (50 mg/kg) consecutively were administered intramuscularly (IM). Anesthetic depth and cardiopulmonary symptoms were monitored starting from the pre-injection moment (T0) till the 60th minute (T60). At T60, atipamezole at a dosage 4 times that of dexmedetomidine was injected intramuscularly to the DX group (320 µg/kg) and the DXK group (160 µg/kg). In the DX group, only minimal sedation, bradycardia, and a sudden drop in respiratory rate were seen (P<0.05). The cardiopulmonary parameter values in the DXK group were affected to a lesser extent compared to the DK group. In the DXK group, 22.47±0.64 minutes after atipamezole injection, all pigeons were on their feet. As a result, it was concluded that dexmedetomidine (80 µg/kg) alone should not be used in pigeons, and if it is needed to be used, cardiopulmonary parameters should be carefully monitored peri-anesthetically. Dexmedetomidine (40 µg/kg) and ketamine (50 mg/kg) can be used in clinical practices that require a moderate level of anesthesia. Atipamezole can safely be used at 4 times the dosage of dexmedetomidine in pigeons.
Keywords: Atipamezole, dexmedetomidine, ketamine, pigeon

Evcil Güvercinlerde Deksmedetomidin ve Deksmedetomidin-Ketamin Kombinasyonunun Anestezik Özellikleri ile Reversal Bir Ajan Olarak Atipamezolün Değerlendirilmesi

Öz: Bu çalışmanın amacı evcil güvercinlerde (Columba livia) deksmedetomidin ve ketaminin tek başına ve deksmedetomidin-ketamin kombinasyonunun anestezik etkinliğini ve α2 adrenerjik antagonisti atipamezolün etkilerini belirlemektir. DX grubuna deksmedetomidin (80 µg/kg), K grubuna ketamin (100 mg/kg) tek başına, DXK grubuna ise deksmedetomidin (40 µg/kg) ve ketamin (50 mg/kg) art arda kasiçi (IM) yolla uygulandı. Anestezi derinliği ile kardiyopulmoner bulgular enjeksiyon öncesinden (T0) 60. dakikaya (T60) kadar izlendi. T60'da IM yolla atipamezol, deksmedetomidinin 4 katı dozda DX (320 µg/kg) ve DXK gruplarına (160 µg/kg) enjekte edildi. DX grubundaki güvercinlerde yalnızca minimal seviyede sedasyon ile bradikardi ve solunum sayısında ani düşme görüldü (P<0.05). DXK grubunda kardiyopulmoner değerler DX grubuna göre daha az etkilendi. DXK grubunda atipamezol enjeksiyonundan 22.47±0.64 dk sonra tüm güvercinler ayaktaydı. Sonuç olarak deksmedetomidin (80 µg/kg) güvercinlerde tek başına kullanılmamalı, kullanım mecburiyetinde kardiyopulmoner parametreler perianestezik olarak dikkatle takip edilmelidir. Deksmedetomidin (40 µg/kg) ve ketamin (50 mg/kg) orta seviyede anestezi gerektiren klinik uygulamalarda kullanılabilir. Atipamezol güvercinlerde deksmedetomidinin dört katı dozda güvenle kullanılabilir.
Anahtar kelimeler: Atipamezol, deksmedetomidin, güvercin, ketamin

Introduction

Pigeon breeding is a hobby and a cultural tradition (Jerolmack, 2007). Pigeons are still used in laboratory studies by veterinary students, in investigations of neurobiological and neuroendocrine mechanisms, and especially in stereotaxic surgery (Baek et al., 2020; Martel et al., 2021). According to data on the use of animals for scientific purposes in EU countries, among the 9,388,162 animals used in scientific research in 2017, avian species constituted 6% (EC, 2019). Surgical interventions in both clinics and scientific studies increase the importance of anesthesia in pigeons.

Until recently, routine clinical anesthesia in avian species used to be based on inhalant anesthesia consisting solely of isoflurane or sevoflurane without

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any additional drugs to ensure fast recovery and avoid potential negative effects of additional drugs. However, although isoflurane and sevoflurane cause loss of consciousness, their effect on the perception of pain stemming from the neural processing of pain stimulants is very little to none. In recent years, injectable anesthetics obtained by adding low doses of dissociative anesthetics to analgesics, tranquilizers, or sedative agents have been used as part of a balanced anesthesia protocol (Hawkins and Paul-Murphy, 2011; Heard, 2016; Lichtenberger and Lennox, 2016; Sandmeier, 2000). Sedative agents constitute a useful alternative to reduce physiological stress in avian species in which painless clinical procedures are applied, and with the use of safe and effective sedative agents, they provide significant benefits to veterinarians and staff (Doss and Mans, 2021; Lennox, 2001; Mans, 2017).

Injectable anesthetics have prominent advantages, such as ease of use, low cost, fast induction, no requirement of expensive equipment, usability under field conditions, and the availability of specific reversal agents to shorten the recovery period (Ludders, 2015). Among injectable anesthetics, ketamine, which is a dissociative anesthetic, and ketamine combinations are frequently used as inductive agents (Hawkins and Pascoe, 2007). Regarding anesthetic depth, although ketamine is used in high doses, it has been reported that it cannot produce a deep level of anesthesia (Gunkel and Lafortune, 2005). Combinations of ketamine alpha 2 (α2) with adrenergic agonists (xylazine, detomidine, medetomidine) have long been used in clinical practice to induce muscle relaxation, reduce the dose of the inductive agent, and ensure immobility for a longer duration. In addition to providing analgesia, α_2 adrenergic agonists also reduce the need for inhalant anesthetics. On the other hand, they have certain negative effects such as potential cardiopulmonary depression. Dexmedetomidine, which has strong sedative and analgesic properties, is the dextro-isomer of medetomidine, and it bonds with α_2 adrenergic receptors more potently and selectively than xylazine or detomidine. Dexmedetomidine, which is approximately 1.6 times as strong as medetomidine, is widely used for premedication as a part of balanced anesthesia in veterinary clinic applications for treatments of small animals (Atalan et al., 2002; Gunkel and Lafortune, 2005; Heard, 2016; Pan, 2021). In the sedation of small animals, atipamezole, which is a specific α_2 reversal agent for dexmedetomidine, is recommended to be used at doses three times as high as those of dexmedetomidine, and it has been reported that its use may cause vomiting, hypersalivation, diarrhea, and tremors (Antisedan, 2022). Research on the dosage of atipamezole as a reversal agent for dexmedetomidine in pigeons is continuing (Hornak et al., 2014).

There have been few studies on the sedative/analgesic effects of dexmedetomidine, which is a reltively new α_2 adrenergic agonist producing strong analgesia in pigeons, the effect duration of atipamezole, which is a specific reversal agent for α_2 adrenergic agonists, and its effect on recovery. Hence, in this study, it was aimed to determine the clinical, reflex-related, and cardiopulmonary effects of dexmedetomidine alone and in combination with ketamine in pigeons and evaluate the effects of atipamezole used at doses 4 times as high as the dose of dexmedetomidine, dexmedetomidine alone, and dexmedetomidine-ketamine combined on the anesthesia and recovery processes.

Materials and Methods

This study was conducted with the ethical approval of the Harran University Animal Experiments Local Ethics Committee dated 11.02.2020 and numbered 2020/001/03 at Harran University Animal Experiments Application and Research Center.

The study included 30 healthy adult pigeons aged between 12 and 24 months with a mean weight of 413±73.77 g. Fifteen days before starting the study, the pigeons were procured from a local business and placed in three separate stainless-steel cages at dimensions of 480x240x180 cm in groups of 10 in the avian species unit of the Animal Experiments Research Center in a quiet and stress-free setting. Clinical examinations of all pigeons were performed, and their respiratory and heart rates, body temperatures, and various physical reflexes were checked. They were kept at a standard room temperature (25°C) and fed ad libitum with water and feed. To prevent any potential adversities that could be caused by the behaviors of different people, the daily needs of the pigeons were met by the same person. The pigeons were observed in terms of eating, drinking, and unusual behaviors in the process before the implementation of the study.

Prior to anesthesia, all pigeons were weighed, and their general health examinations were performed. One hour before injecting drugs, their water and feed consumption was stopped.

To minimize potential stress, the pigeons were left in the experimental environment for about 10 minutes after they were moved from their cages to the aforementioned environment. The data recorded 15 minutes before the first injections were accepted as initial values (T0). Clinical symptoms, reflex scores, and cardiopulmonary findings observed before and during anesthesia were recorded in the anesthesia data form that was previously prepared. Only three pigeons per day (one at a time) were exposed to anesthesia. In the study, each pigeon was used only once.

Anesthesia protocol

All pigeons were randomly assigned to three groups. The pigeons in the DX group were administered dexmedetomidine at a dosage of 80 µg/kg (Sedadomid® 200 mcg/2 ml, Kocak Farma, Tekirdag, Turkey), the pigeons in the K group were injected ketamine at a dosage of 100 mg/kg (Ketasol % 10® 10 ml, Richter Pharma, Wels, Austria), and the pigeons in the DXK group were administered dexmedetomidine at a dosage of 40 µg/kg and ketamine at a dosage of 50 mg/kg consecutively. The dexmedetomidine in the DX group and the ketamine in the K group were slowly injected to the M. pectoralis unilaterally, while the dexmedetomidine and ketamine in DXK group were consecutively and bilaterally injected to the M. pectoralis by using an insulin syringe (30 gauge). Atipamezole, which is an α_2 adrenergic reversal agent, (Antisedan® 10 ml, 5 mg/ml, Orion Pharma, Espoo, Finland) was slowly administered to the DX (320 µg/kg) and DXK (160 µg/kg) groups at the 60th minute (T60) through the same muscle group at a dosage 4 times as high as the dosage of dexmedetomidine. Although dexmedetomidine is a pre-anesthetic with sedative effects, it was used under the category of anesthetics in this study.

Reflexes

To evaluate anesthetic depth, reflexes were scored according to the reflex evaluation scoring system reported by Korbel (AVA, 2004; Korbel, 1998). In the evaluation of findings related to reflexes, eyelid opening, palpebral reflex, pupillary dilatation, pupillary reflex, corneal reflex, head position, neck tone, leg tone, pectoral reflex, wing withdrawal reflex, interphalangeal reflex, and cloacal reflex values were used. (Table 1). All reflexes were observed by the same person who did not know about the drug group that was injected.

Total scores (TS) of 27-29 were classified as a full consciousness state, a score of 24 was categorized as the initiation of sedation, scores of 18-24 were categorized as minimal anesthesia, scores of 14-18 were categorized as mild anesthesia, scores of 5-13 were categorized as moderate anesthesia, and scores of 2-4 were categorized as deep anesthesia (AVA, 2004; Hornak et al., 2014; Korbel, 1998; Sandmeier, 2000).

Reflexes were checked in all groups 15 minutes before anesthetic injection (T0) and at the 5th (T5), 10th (T10), 15th (T15), 20th (T20), 25th (T25), 30th (T30), 40th (T40), 50th (T50), and 60th (T60) minutes of injection. Atipamezole was injected in the DX and DXK groups immediately after reflex scoring was completed at T60. At the 5th (AT5), 10th (AT10), and 20th (AT20) minutes after atipamezole injection, reflex scoring was continued, and the scores were recorded. No injection was administered to the pigeons in the K group at T60.

Table 1. Reflex scoring table used to determine anesthesia levels (AVA, 2004; Korbel, 1998)

Parameter	Reflex Score (Point)	Stimulation and Evaluation of Reflexes
Eyelid opening	0: Eyelid closed; 1: Eyelid partially closed; 2: Eyelid open	It was assumed that as the anesthetic depth increased, the opening of the eyelids was closed
Palpebral reflex	0: No reflex; 1: Reflex without head movements; 2: Reflex with head movements	Evaluated by touching the eyelid border in medial cantus with a dry cotton swab
Pupillary dilatation	0: Mydriasis; 1: Pupillary openness 50-75%; 2: Miosis	Relative widening of the pupil. It was assumed that as anesthesia deepened, pupils would gradually widen
Pupillary reflex	0: No reflex; 1: Delayed reflex; 2: Physiological	Holding a source of light from 0.5 cm into the eye, the rate and degree of pupillary reflex were evaluated
Corneal reflex	0: No reflex; 1: Delayed reflex; full closure of nictitating membrane; 2: Delayed reflex; partial closure of nictitating membrane; 3: Physiological reflex	Holding the eyelid open, reaction of nictitating membrane at the peripheral contact of cornea was observed by using a dry, sterile swab
Head position	1: Loose sagging; 2: Light elevation; 3: Head raising	Sensitivity was evaluated according to the loose position of head without the effect of a specific stimulant
Neck tone	0: None; 1: Present	Sensitivity was evaluated by slightly moving the head
Leg tone	0: None; 1: Low tone; 2: Contraction; 3: Contraction and defensive movement	Depth sensitivity was evaluated based on reactions following muscle tone and passive stretching of legs
Pectoral reflex	0: No reflex; 1: Slight wing movement; 2: Movements of various parts of the body (Leg/wing movements, head movement, eyelid opening); 3: Big reactions	Skin between ossa pubis was squeezed one degree with a set of mosquito forceps and evaluated with repeated constant pressure
Wing withdrawal reflex	0: No reflex; 1: Slight wing movement; 2: Movements of various parts of the body (Leg/wing movements, head movement, eyelid opening); 3: Big defensive reactions	Evaluated by squeezing the front part of radius-ulna on the wing with fingertips
Interphalangeal reflex	0: No reflex; 1: Slight leg pulling; 2: Noticeable leg movement, head movements, eye opening; 3: Substantial defensive reactions	Evaluated by pinching the skin between the phalanges
Cloacal reflex	0: No reflex; 1: Sphincter contraction, slow leg movement; 2: Muscle retraction, head movements, eye opening; 3: Substantial defensive reactions	Evaluated by squeezing the pericloacal skin with fingertips

Cardiopulmonary parameters

As cardiopulmonary signs, heart rate (HR), indirect mean blood pressure (IBP), respiratory rate (RR), oxygen saturation (SpO_2), end-tidal carbon dioxide ($EtCO_2$), and cloacal temperature (CT) data were monitored using a multiparametric monitor (Mindray UMEC12VET, Shenzhen Mindray Bio-Medical Electronics Co, Shenzhen, People's Republic of China). Accordingly, cardiopulmonary parameters were recorded in all groups at T0, T5, T10, T15, T20, T25, T30, T40, T50, and T60. To prevent the cardiopulmonary parameters from being affected at the follow-up time spots, reflexes were checked after cardiopulmonary parameter values were recorded. In the initial period of anesthesia, cardiopulmonary parameter values were recorded at 5-minute intervals until T30. In the DX and DXK groups, these values were recorded at AT5, AT10, and AT20. As no injection was administered to the pigeons in the K group, data were recorded only until T60.

In the monitoring of cardiopulmonary parameter values, an assistant was employed. The assistant held the pigeons in the supine position, opened the wings to the sides and pulled the legs slightly backwards, a yellow electrode was fixed on the skin at the base of the left wing, a red electrode was fixed on the skin at the base of the right wing, and a green electrode was fixed on the skin fold close to the proximal of the M. gastrocnemius on the left leg. I, II, and II derivations, unipolar extremity derivations including aVR, aVL, and aVF, and standard bipolar derivation systems were used (Mindray 562a, People's Republic of China). All recordings were calibrated to 1 mV/10 mm. IBP measurements were performed indirectly. For this purpose, a medium-sized avian IBP cuff was placed on the dorsal metatarsal artery on the right leg (Mindray Cm 1500D, People's Republic of China). Cuff width was adjusted to 40% of the leg circumference. For SpO_2 monitoring, a pulse oximeter probe was fixed on the muscle mass on right radius (Mindray 562a, People's Republic of China). In the $EtCO_2$ measurements, an $EtCO_2$ tube was placed on the nose, covering the whole beak, and the values were observed on the monitor (Mindray Cm 1500 Series, People's Republic of China). Throughout the anesthesia period, no additional O_2 was provided to the pigeons in any group. CT was monitored using a thermometer placed in the cloaca (Mindray MR402B, People's Republic of China).

Statistical analyses

In all analyses, the JMP 14 software was employed. The data were statistically analyzed with Levene's test for variance homogeneity assumptions and the Shapiro-Wilk test for normal distribution assumptions ($P>0.05$). Hence, repeated-measures analysis of variance (ANOVA) and Tukey's HSD multiple comparison test were used to determine whether there were any significant differences between the groups. The data are presented as median in Table 2 and Mean±St Deviation in Table 3. The level of statistical significance was set at $P<0.05$ in all tests.

Results

Clinical findings

For the pigeons in the DX group, first sedation symptoms were observed at the 8th minute with signs of decrease in eyelid opening and inability to hold the head, and induction was achieved at a mean time of 12.56±0.70 minutes. In two of the pigeons, (pigeons 4 and 7), along with convulsion that started at the 3rd and 12th minutes and lasted approximately 2 minutes, second-degree atrioventricular block, arrythmia, and respiration irregularity signs were observed. At the 2nd minute of atipamezole injection, 3 pigeons (pigeons 2, 5, and 9) rose to their feet, and at a mean time of 5.06±0.87 minutes, all pigeons were on their feet. An increase in P wave duration and amplitude in ECG and prolongations in P-R intervals were noted. Starting from AT5, P, Q, and R values returned to their initial levels.

In the pigeons in the K group, along with symptoms of pupillary dilatation, inability to hold the head, and incoordination, anesthesia symptoms started to be seen, and anesthesia was induced at a mean time of 5.23±0.38 minutes. The pigeons were observed to be unexcited during their entry into anesthesia or in recovery. No significant change was observed in their P, Q, R, and S values in ECG. Arrythmia developed in two pigeons (pigeons 6 and 9), but these arrythmias disappeared by T50 spontaneously.

In the pigeons in the DXK group, along with symptoms of a decrease in eyelid opening and inability to hold the head, anesthesia symptoms started to be seen at the 5th minute, and anesthesia was induced at a mean time of 10.16±0.37 minutes. Second-degree atrioventricular block, arrythmia, and irregularities in respiration frequency were seen in two pigeons (pigeons 2 and 8) between minutes 9 and 15 and one pigeon (pigeon 5) between minutes 15 and 33 (Figure 1).

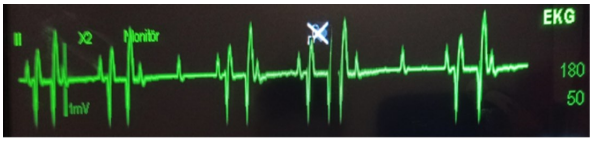

Figure. 1. ECG trace and atrioventricular block of Pigeon 5 in DXK.

Defensive movements were observed in four pigeons (pigeons 1, 5, 6, and 8), while their reflexes were being checked between minutes 10 and 30. At the 3rd minute of atipamezole injection, temporary tremors

Table 2. Reflex scores for anesthesia levels in 10 pigeons which were administered IM DX, K, and DXK and atipamezole at minute 60 and time-dependent median results of the total score (TS)

VB	TM	T0	T5	T10	T20	T30	T40	T50	T60	AT5	AT10	AT20
Eyelid gap	**DX**	2	2	1	1	1	1	1	1	2	2	2
	K	2	2	1	1	2	2	2	2	-	-	-
	DXK	2	1	0	0	0	0	0	0	2	2	2
Palpebral reflex	**DX**	2	1	1	0	0	1	1	1	2	2	2
	K	2	1	1	1	1	1	1	2	-	-	-
	DXK	2	2	0	0	0	0	0	1	2	2	2
Pupillary dilatation	**DX**	2	2	2	1	1	1	1	2	2	2	2
	K	2	1	1	1	1	1	2	2	-	-	-
	DXK	2	2	1	1	1	1	1	1	2	2	2
Pupillary reflex	**DX**	2	2	2	2	2	2	2	2	2	2	2
	K	2	2	1	1	2	2	2	2	-	-	-
	DXK	2	2	1	1	1	1	1	1	2	2	2
Corneal reflex	**DX**	3	3	2	2	2	2	3	3	3	3	3
	K	3	2	2	2	2	2	3	3	-	-	-
	DXK	3	3	2	2	2	2	2	2	3	3	3
Head position	**DX**	2	2	1	1	1	1	1	1	2	2	2
	K	2	0	0	0	0	0	1	1	-	-	-
	DXK	2	0	0	0	0	0	0	0	1	1	2
Neck tone	**DX**	1	1	1	1	1	1	1	1	1	1	1
	K	1	0	0	0	0	1	1	1	-	-	-
	DXK	1	1	0	0	0	0	0	0	1	1	1
Leg tone	**DX**	2	3	3	3	2	3	3	3	3	2	2
	K	3	1	1	1	2	2	2	2	-	-	-
	DXK	2	1	0	1	1	2	2	2	2	2	2
Pectoral reflex	**DX**	3	3	3	3	3	3	3	3	2	2	3
	K	3	1	2	2	2	2	2	2	-	-	-
	DXK	3	2	2	2	2	2	2	2	1	1	1
Wing withdrawal reflex	**DX**	2	3	3	2	2	2	2	3	2	2	3
	K	3	2	2	2	2	2	2	2	-	-	-
	DXK	3	1	2	2	1	0	2	1	1	0	0
Interphalangeal reflex	**DX**	2	3	3	2	2	2	2	3	3	2	3
	K	3	1	1	2	2	2	2	2	-	-	-
	DXK	2	1	1	0	0	0	1	1	0	0	1
Cloacal reflex	**DX**	3	3	3	3	2	3	3	3	2	2	2
	K	3	1	1	1	2	2	2	2	-	-	-
	DXK	3	2	1	1	1	1	2	2	1	1	1
Total score	**DX**	27.00^{a}	25.50^{abc}	23.00^{bcd}	20.50^{ef}	19.50^{f}	20.50^{def}	21.00^{cde}	21.50^{bcd}	25.50^{bcd}	24.00^{abc}	26.00^{ab}
	K	28^{a}	13^{e}	12^{e}	14^{e}	16^{d}	18^{d}	20^{c}	22^{b}	-	-	-
	DXK	27^{a}	15.50^{bcde}	11.50^{cde}	10.00^{de}	10.75^{e}	11.75^{de}	12.25^{cde}	14.50^{bcde}	15.250^{bcd}	18.50^{ab}	18.50^{bc}

VB: Variable; TM: Treatment; DX: Dexmedetomidine 80 µg/kg; K: Ketamine 100 mg/kg; DXK: Dexmedetomidine 40 µg/kg and ketamine 50 mg/kg; Atipamezole: 320 µg/kg for DX, 160 µg/kg for DXK.
T0: Baseline, 15 min before anesthetic injection; T5, 10, 20, 30, 40, 50, 60: minutes after T0; AT5, AT10, AT20: Minutes after atipamezole injection at T60.
^{abcdef} *Statistically significant in intragroup evaluations with respect to T0 value (P<0.05). Reflex scores and TS data are presented as median values.*

that lasted about 1 minute were seen in four pigeons (pigeons 2, 3, 6, and 10). All other recoveries were observed to be calm and smooth, and all pigeons were on their feet at a mean time of 22.47±0.64 minutes, but they were lightly drowsy. An increase in P wave duration and amplitude in ECG and prominent prolongations in P-R and R-R intervals were observed. While the arrhythmias that developed in three pigeons (pigeons 2, 5, and 8) disappeared before atipamezole injection, P, Q, and R values returned to their initial levels following of AT5.

Reflex findings

In the examinations in terms of TS, the pigeons in the DX group showed sedation symptoms at the minimal level only in the middle of sedation (19.50 at T30). Along with atipamezole injection, TS (25.50 at AT5) suddenly returned to the initial values ($P<0.05$). It was noted that there were symptoms of convulsions and respiratory irregularities in the DX group. In the pigeons in the K group, a moderate depth of anesthesia was induced in a short time (13.00 at T5), but this level lasted only 15 minutes. In the DXK group, anesthesia started at T10 (11.50 at T10), and a moderate depth of anesthesia was induced (14.50 at T60). In five minutes following atipamezole injection, a mild level of anesthesia was seen (15.25 at AT5) ($P<0.05$). The moderate TS (from T10 to T60) achieved in the DXK group was lower compared to that in the K group. The reflex scores and TS data of the DX, K, and DXK groups are presented in Table 2.

Cardiopulmonary findings

High initial HR values were prominent in all groups. In the DX and DXK groups, following dexmedetomidine injection, dramatic decreases in HR were observed ($P<0.05$), but these dramatic decreases disappeared in 5 minutes as a result of atipamezole injection ($P<0.05$). In the K group, ketamine injection did not significantly affect HR ($P>0.05$). In both the intragroup and intergroup evaluations, dexmedetomidine, ketamine, and dexmedetomidine-ketamine injections did not significantly affect IBP ($P>0.05$).

In the DX and DXK groups, dexmedetomidine led to dramatic decreases in RR immediately after injection ($P<0.05$), but these dramatic decreases disappeared in 5 minutes after atipamezole injection. In the K group, ketamine injection did not significantly affect RR ($P>0.05$). The dexmedetomidine in the DX group and the ketamine in the K group did not significantly affect SpO_2 ($P>0.05$). It was also determined that the dexmedetomidine-ketamine injections in the DXK group could create statistically significant differences, albeit clinically insignificant ($P<0.05$). Dexmedetomidine, ketamine, and dexmedetomidine-ketamine injections did not significantly affect $EtCO_2$ values ($P>0.05$).

Dexmedetomidine, ketamine, and dexmedetomidine-ketamine injections significantly reduced CT in the pigeons ($P<0.05$). Atipamezole led to an increase in CT in both groups only after 10 minutes (at AT10, 40.37°C in DX, 39.08°C in DXK) ($P<0.05$). The cardiopulmonary parameter data of the DX, K, and DXK groups are presented in Table 3.

Table 3. Time-dependent mean±standard deviation results of cardiopulmonary variables in 10 pigeons which were administered IM DX, K, and DXK and atipamezole at minute 60

Variable	Treat-ment	T0	T5	T10	T15	T20	T25	T30	T40	T50	T60	AT5	AT10	AT20
HR (beats/ minute)	DX	254.9 ±100. 74^{A}	136.4±5 2.62^{Bc}	134.7±1 26.0^{Bc}	120.2±8 4.2^{Bc}	119.6±1 09.1^{Bc}	112.5±9 7.2^{Bc}	110.7±8 8.5^{Bc}	107.6±8 8.4^{Bc}	106.1±8 8.6^{Bc}	103.0±7 3.6^{Bc}	253.6±9 5.9^{A}	271.8±1 06.9^{A}	272.8±1 37.4^{A}
	K	236.8 ±31.5^{A}	258.8±5 3.0^{A}	231.0±5 3.9^{A}	234.4±5 0.4^{A}	237.5±5 2.3^{A}	225.6±4 0.2^{A}	225.3±3 9.6^{A}	225.3±3 9.6^{A}	239.7±5 0.6^{A}	221.3±5 1.6^{A}	-	-	-
	DXK	266.8 ±14.9^{A}	137.2±9. 5^{Cb}	115.3±6. 5^{CDb}	109.4±5. 8^{CDb}	100.8±7. 3^{CDb}	99.7±6.0 Db	112.9±1 0.4^{CDb}	98.0±6.2 Db	102.2±8. 2^{CDb}	96.3±7.4 Db	271.2±1 1.5^{A}	246.8±1 1.1^{AB}	222.5±1 0.6^{Ba}
IBP (mm/ Hg)	DX	91.6± 131.4^{A}	90.0±85. 3^{A}	93.7±11 1.1^{A}	85.6±80. 8^{A}	90.1±81. 9^{A}	98.5±78. 1^{A}	93.2±12 8.6^{A}	111.1±1 47.0^{A}	108.8±9 9.9^{A}	90.8±10 8.0^{A}	113.7±1 12.5^{A}	113.3±1 09.5^{A}	117.8±1 01.8^{A}
	K	90.5± 11.1^{A}	101.6±9. 5^{A}	87.2±5.9 A	89.1±7.6 A	87.0±7.6 A	93.0±11. 4^{A}	95.8±9.0 6^{A}	87.0±9.0 A	98.4±11. 4^{A}	78.4±10. 6^{A}	-	-	-
	DXK	102.4 ±11.6^{A}	104.0±8. 7^{A}	109.3±6. 9^{A}	105.6±1 1.4^{A}	105.8±8. 840^{A}	91.8±7.7 A	100.9±8. 9^{A}	94.0±9.9 A	90.4±8.4 A	94.0±8.0 A	114.5±1 1.6^{A}	112.1±1 1.1^{A}	113.7±8. 6^{A}
RR (breaths /minute)	DX	59.3± 34.2^{A}	40.4±36. 9^{BCDE}	37.4±43. 3^{BCDEc}	31.5±44. 6^{Ec}	35.2±91. 2^{CDE}	33.6±67. 2DE	33.4±60. 7DE	31.2±48. 7^{Ec}	29.5±49. 5^{Ec}	26.1±38. 3^{Ec}	54.1±51. 9^{AB}	52.1±30. 2^{ABC}	49.7±31. 2^{ABCD}
	K	49.9± 3.2^{A}	48.2±4.9 A	49.9±3.0 A	51.7±3.7 A	51.5±4.4 A	44.0±4.4 A	55.5±4.5 A	47.6±4.0 A	48.5±4.2 A	53.8±8.0 A	-	-	-
	DXK	64.6± 4.7^{ABb}	43.7±2.8 CD	49.8±3.1 ABCD	50.5±5.3 ABCDa	49.0±5.5 BCD	46.6±4.8 CD	45.4±5.2 CD	41.9±3.8 D	40.4±4.3 D	35.2±2.3 D	64.9±5.1 AB	65.8±5.3 Aa	60.2±4.6 ABC
SpO_2 (%)	DX	89.7± 15.4^{A}	93.6±6.0 Ac	89.9±16. 4^{Ac}	91.8±11. 4^{Ac}	89.1±23. 5^{A}	88.5±41. 8^{A}	89.9±24. 4^{A}	90.6±24. 7^{A}	89.6±34. 0^{A}	93.8±11. 9^{Ac}	87.4±23. 9^{A}	87.6±23. 8^{A}	90.0±13. 7^{A}
	K	88.2± 1.5^{A}	74.9±4.2 A	80.8±3.2 A	84.2±2.3 A	82.5±1.8 A	83.4±2.8 A	82.7±3.2 A	83.1±3.1 A	84.1±3.5 A	83.5±3.5 A	-	-	-
	DXK	88.7± 1.8^{AB}	89.3±0.9 Ab	87.9±1.8 AB	87.9±1.6 AB	88.8±1.8 AB	89.1±1.3 A	83.9±3.3 AB	87.4±2.0 AB	90.4±1.9 A	90.4±1.5 A	82.9±3.5 AB	79.1±3.2 B	82.6±2.4 ABa
$EtCO_2$ (mm/ Hg)	DX	41.8± 20.7^{Ac}	37.5±25. 5^{A}	42.8±33. 3^{A}	42.3±33. 9^{A}	40.4±32. 1^{A}	42.5±32. 2^{A}	42.4±38. 0^{A}	41.2±33. 8^{A}	41.0±34. 3^{A}	39.6±33. 8^{A}	43.1±22. 8^{A}	43.1±26. 8^{A}	43.5±18. 4^{A}
	K	33.1± 3.4^{A}	32.6±2.5 A	34.9±2.5 A	34.5±2.8 A	39.1±2.0 A	35.5±2.2 A	38.8±2.6 A	36.4±2.1 A	37.4±2.9 A	34.7±2.2 A	-	-	-
	DXK	40.9± 1.5^{A}	36.8±6.5 A	33.0±1.8 Aa	32.7±1.5 Aa	37.3±2.5 A	36.7±1.3 A	37.3±2.1 A	34.7±2.2 A	36.9±2.2 A	35.4±1.7 A	39.8±2.0 A	38.6±2.5 A	40.5±2.6 A
CT (°C)	DX	42.3± 0.7^{A}	42.1±1.0 Ac	41.9±1.0 ABc	41.8±1.2 ABC	41.5±1.3 BC	41.2±1.4 CD	40.9±1.2 DE	40.4±1.5 EF	40.0±1.9 FG	39.7±2.2 G	39.5±2.6 G	40.4±2.8 EF	40.8±2.9 DE
	K	41.9± 0.2^{A}	41.4±0.3 AB	41.2±0.3 ABC	41.1±0.3 ABCD	40.9±0.3 ABCD	40.7±0.4 BCD	40.7±0.5 BCD	40.4±0.6 BCD	40.1±0.5 D	40.2±0.7 CD	-	-	-
	DXK	42.4± 0.1^{Ab}	42.4±0.1 Ab	41.9±0.2 ABb	41.6±0.2 B	41.2±0.2 BC	40.8±0.1 CD	40.2±0.2 DE	39.6±0.1 EF	38.8±0.2 GHb	38.5±0.2 GHb	38.2±0.2 Ha	39.1±0.3 FGa	40.3±0.4 DE

DX: Dexmedetomidine 80 µg/kg; K: Ketamine 100 mg/kg; DXK: Dexmedetomidine 40 µg/kg and ketamine 50 mg/kg; Atipamezole: 320 µg/kg for DX, 160 µg/kg for DXK. HR: Heart rate; IBP: Indirect mean blood pressure; RR: Respiratory rate; SpO_2: Oxy-hemoglobin saturation; $EtCO_2$: End-tidal CO_2; CT: Cloacal temperature. T0: Baseline, 15 min before anesthetic injection; T5, 10, 15, 20, 25, 30, 40, 50, 60: minutes after T0; AT5, AT10, AT20: Minutes after atipamezole injection at T60.

^{ABCD} Statistically significant in intragroup evaluations with respect to T0 value (P<0.05).

[a] Difference between DXK and DX groups at specified time point is significant (P<0.05). [b] Difference between DXK and K groups at specified time point is significant (P<0.05).

[c] Difference between DX and K groups at specified time point is significant (P<0.05).

Discussion and Conclusion

Dexmedetomidine is a relatively new α_2 adrenergic agonist, and it is an agent that supports anesthesia with its sedative, analgesic, and hypnotic properties. As dexmedetomidine is recommended at half the dosage of medetomidine, studies on medetomidine were also considered in determining the dosages of dexmedetomidine (Heard, 2016; Posner, 2018). The dosages used in this study were determined according to studies conducted on dexmedetomidine, medetomidine (Hornak et al., 2014; Pollock, 2001), ketamine (Azizpour and Hassani, 2012; Gunkel and Lafortune, 2005; Kamiloglu et al., 2008), their different combinations (Lumeij and Deenik, 2003; Memon et al., 2021), and atipamezole (Hornak et al., 2014; Lumeij and Deenik, 2003) injected to pigeons through the IM route. In previous studies, ketamine was used alone through the IM route in the dosage range of 20-50 mg/kg (Azizpour and Hassani, 2012; Gunkel and Lafortune, 2005; Kamiloglu et al., 2008). The ketamine dose used in the present study (100 mg/kg) was accepted as a high dosage for pigeons based on the information in the literature. As it is recommended to use atipamezole at a dosage three times that of dexmedetomidine following dexmedetomidine sedation in dogs, the atipamezole injected in the present study was administered at a dosage 4 times that of dexmedetomidine in the pigeons (320 µg/kg in DX, 160 µg/kg in DXK) (Antisedan, 2022).

The results of studies on pigeons in which α_2 agonists were used on their own have some similarities in terms of cardiopulmonary parameter values, cloacal temperatures, and sedative effects. It has been argued that these agents lead to bradycardia and respiratory depression and provide inadequate sedation, and therefore, they should be used only for holding and procedures involving little pain. The same researchers have also emphasized that α_2 agonists used alone lead to time-dependent hypothermia (Duranni et al., 2008; Duranni et al., 2009; Pollock et al., 2001; Sandmeier, 2000). The findings obtained in this study were consistent with the results of the researchers who have stated that pigeons are relatively resistant to α_2 adrenergic agonists (Duranni et al., 2008; Duranni et al., 2009; Pollock et al., 2001; Sandmeier, 2000). Additionally, studies conducted on medetomidine showed that the dosage used in this study was low, and medetomidine could be researched at higher dosages (Pollock et al., 2001; Sandmeier, 2000). It was determined to be necessary in this study to carefully monitor cardiopulmonary variables and keep atipamezole available starting from the moment of injection when dexmedetomidine is used alone, even at dosages that are not very high (80 µg/kg, IM).

It was reported that a low dosage of ketamine (30 mg/kg) used alone led to excitement in pigeons during their entry into anesthesia, it did not provide a sufficient loss in the pedal reflex, adequate muscle relaxation was not observed in anesthesia, and a decrease was seen in body temperature (Azizpour and Hassani, 2012). In a study in which ketamine was injected through the intraosseous (IO) and IM paths, it was emphasized that induction was achieved at a mean time of 7.5±0.8 minutes through IM, recovery was achieved at a mean time of 90±12 minutes, and ketamine provided a satisfactory level of anesthesia in pigeons at a dosage of 50 mg/kg (Kamiloglu et al., 2008). In this study, although no adverse behaviors were observed in most of the pigeons during their entry into anesthesia and recovery in the K and DXK groups which were administered ketamine, the moderate level of anesthesia that was achieved was quite far from the 2-4-point interval in the anesthesia scoring system, which shows a depth of anesthesia on the surgical level. While similarities to the findings of other researchers were observed in terms of induction durations and cardiopulmonary values (Azizpour and Hassani, 2012; Kamiloglu et al., 2008), ketamine that was used at two times (100 mg/kg) the dosage used in the study conducted by Kamiloglu et al. (2008) showed a shorter effect in terms of recovery duration. It was thought that at both low and high dosages, ketamine induced anesthesia for similar durations.

It was reported that medetomidine-ketamine anesthesia provided smooth and unexciting anesthesia induction, the duration of anesthesia was 55.79±4.51 minutes, and HR, RR, and CT considerably decreased during anesthesia (Memon et al., 2021). In the experimental and clinical study conducted by Lumeij and Deenik (2003), results in medetomidine-ketamine anesthesia showed differences (Lumeij and Deenik, 2003). In their experimental research, the researchers observed deep anesthesia, a fast and smooth recovery, as well as significant differences in terms of reflex scores and HR. In their clinical research, on the other hand, it was determined that the medetomidine-ketamine combination led to unsafe anesthesia as a result of severe wing movement behaviors, and it was therefore emphasized that more controlled studies should be conducted in the clinical environment before making practical recommendations regarding the use of this combination (Lumeij and Deenik, 2003). It was reported that when inhalant anesthetics (isoflurane and sevoflurane) were used in avian species at higher concentrations than required, especially as the sole agent, they lead to apnea and hypotension, and they could not provide antinociception despite creating a loss of consciousness. The use of low-dosage sedative agents and dissociative anesthetics is recommended in the peri-anesthetic period before using inhalant anesthetics as a part of balanced anesthesia due to analgesia, need for comfort, and the long-term effects of subacute and chron-

ic nociception. The characteristics of dexmedetomidine (40 µg/kg) and ketamine (50 mg/kg) anesthesia at the dosages that were used in this study showed similarities to the findings of other studies in terms of HR, RR, and CT, and these dosages provided shorter anesthesia durations (Lumeij and Deenik, 2003; Memon et al., 2021). In this study, it was observed that dexmedetomidine led to a greater degree of decrease in CT compared to ketamine. While all reflexes and cardiopulmonary parameter values except for CT in the groups in which atipamezole was used (DX and DXK) returned to the T0 values within five minutes following atipamezole injection, it was seen that CT started to increase in both groups only at the 10^{th} minute. Although the moderate level of anesthesia obtained using the dexmedetomidine-ketamine combination had a lower score compared to ketamine anesthesia alone, it was seen that it did not fall to the 2-4-point interval, which is required for performing surgery. It was considered that this anesthesia could be used in clinical applications that require a moderate level of anesthesia depth or before inhalant anesthesia as a part of balanced anesthesia due to the analgesic property of dexmedetomidine (Heard, 2016; Lichtenberger and Lennox, 2016). Considering its anesthetic effects, it was concluded that as reported by Lumeij and Deenik (2003), before making any practical recommendations on the use of a dexmedetomidine-ketamine combination, more controlled studies in clinical environments should be conducted. It was suggested that anesthesia with ketamine could not be achieved at the desired level and duration without combining it with dexmedetomidine, and this combination could be used in short-lasting procedures such as sample collection, radiography, ultrasonography, and bandage application.

In all studies conducted with different dosages of atipamezole in pigeons, the researchers reported that it provided rapid and smooth recovery from anesthesia by reversing the effects of α_2 adrenergic agonists (Hornak et al., 2014; Sandmeier, 2000). Hornak et al. (2014), stated that atipamezole reversed most sedation and cardiorespiratory side effects in 10 minutes after the induction made with a midazolam-dexmedetomidine combination, and it was only late in terms of increasing CT. Memon et al. (2021), emphasized that in medetomidine-ketamine anesthesia, atipamezole administered at half the dosage of medetomidine shortened anesthesia duration in pigeons by 18 minutes. It has been reported that flumazenil, which is a reversal agent of benzodiazepine, can be used in avian species to partially or fully reverse the effects of diazepam or midazolam, but due to its short half-life, dosage repletion might be needed (Doss and Mans, 2021; Heard, 2016; Mans, 2017; Martel et al., 2021). In this study, consistently with other results in the relevant literature, atipamezole administered at a dosage 4 times the dosage of dexmedetomidine was quickly absorbed following IM injection, and it provided smooth recovery in the DX group at minute 5.06±0.87 and in the DXK group at minute 22.47±0.64 (Hornak et al., 2014; Memon et al., 2021; Sandmeier, 2000). Unlike flumazenil, no dosage repletion was needed (Doss and Mans, 2021; Heard, 2016; Mans, 2017). No vomiting was observed in the DX and DXK groups following the atipamezole injection, but temporary tremors which lasted about one minute in two pigeons in the DX group and four pigeons in the DXK group were considered negative effects of atipamezole. In light of the findings obtained in this study, it was thought that atipamezole administered 4 times the dosage of dexmedetomidine can be safely used in pigeons.

In conclusion, dexmedetomidine should not be used alone in pigeons, even at low dosages (80 µg/kg), and if it has to be used, cardiopulmonary status should be carefully monitored peri-anesthetically. The most significant advantage of dexmedetomidine is that it provides rapid and smooth recovery within 5 minutes with atipamezole injection. Ketamine administered at a high dosage (100 mg/kg) does not affect cardiopulmonary parameter values significantly, but it does not provide deep and long anesthesia for surgery either. As the combination of dexmedetomidine (40 µg/kg) and ketamine (50 mg/kg) in this study did not provide anesthesia deep enough for surgery, it can be used in short-lasting clinical procedures that require only a moderate level of anesthesia or before inhalant anesthesia as a part of balanced anesthesia. Atipamezole can reverse the effects of dexmedetomidine alone or its combination with ketamine when applied at a dosage 4 times that of dexmedetomidine, and it provides a safe, calm, and smooth recovery in pigeons.

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