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Evaluation of hemodynamic, hematological parameters and the clinical effects of dexmedetomidine-ketamine and xylazine-ketamine anesthesia in rabbits

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Abstract: With this study, it was aimed to assess the effects of experimentally induced dexmedetomidine-ketamine (DK) and xylazine-ketamine (XK) combinations on clinical parameters and hemodynamic and hematological parameters in rabbits. In the study, 16 male New Zealand breed rabbits were divided into two groups. Group DK (n = 8) was administered dexmedetomidine (25 µg/kg) and ketamine (30 mg/kg) in the same injector, and Group XK (n = 8) was administered xylazine (4 mg/kg) and ketamine (30 mg/kg) in the same injector through the intramuscular (IM) route. Following the injection, the rabbits' reflexes were tested approximately every 30 s. Hemodynamic parameters were determined before the injection (0 min) and 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 min after the anesthetic combinations were injected. Furthermore, blood gas and electrolyte values were analyzed before, during and after anesthesia. The differences between the groups were not statistically significant in terms of the loss and return times of the righting reflex, ear-pinch reflex and pedal withdrawal reflex ($P > 0.05$). The mean surgical anesthesia duration was determined as 115 min in the DK group and 116.5 min in the XK group. In both groups, the heart rate (HR), respiratory rate (RR), mean arterial pressure (MAP) and arterial oxygen saturation of hemoglobin (SpO_2) decreases. In the statistical analysis, the differences between the groups were statistically significant in terms of HR at the 5th, 10th and 15th min and in terms of SpO_2 at the 120th min ($P < 0.05$). In the DK group, the change in RR based on the pre-injection time (0 min) was found significant ($P < 0.05$). In the statistical analyses on the arterial blood gases and electrolyte findings, the differences between the DK and XK groups were insignificant in terms of pH, pCO_2 and pO_2 ($P > 0.05$) and significant in terms of only glucose (mg/dL) at the 5th min ($P < 0.05$). Consequently, it was observed that the DK and XK combinations had similar effects in healthy adult rabbits regarding the reflex findings, anesthesia duration and hemodynamic and hematological parameters. It was concluded that, to prevent hypoxemia related to RR decrease in the combination of α2 adrenergic agonists and ketamine, there is a need for oxygen reinforcement starting with the induction of anesthesia, and the DK combination needs to be used carefully in patients with respiratory depression.

Key words: Anesthesia, blood gases, dexmedetomidine, hemodynamic parameters, ketamine, reflex times

1. Introduction

Several injectable anesthetic agents and combinations are studies for achieving safe anesthesia in rabbits. Achievement of an ideal anesthesia that provides sufficient muscle relaxation and analgesia and has low complication and mortality rates varies depending on the anesthesia protocol of the agents that are used in combination [1,2].

Ketamine, which is used as a general anesthetic, is a dissociative agent that induces loss of consciousness, indifference to the environment and analgesia in a dose-dependent way. Its side effects in the respiratory and cardiovascular systems at clinically effective doses are minimal. As ketamine does not provide sufficient muscle relaxation when it is used by itself and for preventing cramps and convulsion-like symptoms during recovery, it necessitates usage of preanesthetic agents [3–5].

Agents in the α2 adrenoceptor agonists group (xylazine, medetomidine, dexmedetomidine) are used in combinations as preanesthetic agents before ketamine injection due to their sedative, analgesic, anxiolysis, hypnotic and sympatholytic properties [6–8]. While the clinical effects of agents in this group show difference based on α1 and α2 receptor affinity, they may induce significant side effects on the respiratory and cardiovascular systems [2,7,9–11].

Dexmedetomidine is a highly selective, α2 adrenoceptor agonist preanesthetic agent. It is a pharmacologically active isomer of medetomidine, and it does not contain the

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inactive enantiomer levomedetomidine in its structure. It has a potent activity 2 times higher than medetomidine and 40 times higher than xylazine. In surgical anesthesia, it provides a very good level of muscle relaxation and analgesia. It may lead to dose-dependent hypotension, bradycardia and respiratory depression in rabbits [3,6,12,13].

This study aimed to evaluate the anesthetic effects of the DK and XK combinations in rabbits by using clinical parameters, as well as hemodynamic and hematological parameters.

2. Materials and methods

This study was carried out at the Animal Experiments Implementation and Research Center (HDAM) with the approval of the Harran University Animal Experiments Local Ethics Board (HRÜ - HADYEK) dated 26.02.2018 and numbered 2018/002/01-08.

2.1. Animals

Sixteen 11–12 months old, male New Zealand breed rabbits with weights in the range of 2500–3000 g were used in the study. A week before the study, adaptation of the rabbits to the laboratory conditions was provided. The rabbits were kept in a group in a room containing wood shavings on the ground at a temperature of 20 ± 2 °C, humidity of 50%–60% and a light-dark cycle of 12–12 h and fed with commercial pellet feed and ad libitum water. Before the study, clinical examination of the rabbits was performed, and they were weighed on a precision scale.

2.2. Anesthesia protocol

The 16 New Zealand adult rabbits were randomly divided into two groups. Group DK (n = 8) was given a 25-µg/kg dose of dexmedetomidine (Hipnodex® fliptop vials 200 mcg/2 ml, Haver Farma İlaç A.Ş., İstanbul, Turkey) and a 30-mg/kg dose of ketamine (Alfamine %10® injection, Alfasan International B.V., JA Woerden, Netherlands), while Group XK (n = 8) was given a 4-mg/kg dose of xylazine (Alfazyne %2® injection, Alfasan International B.V.) and a 30-mg/kg dose of ketamine (Alfamine %10® injection, Alfasan International B.V.). All drugs were mixed in a single syringe and given as a single IM injection into the *Mm. quadriceps femoris*.

To prevent pain during catheter application, 45 min before the induction of anesthesia, a local anesthetic pomade (Anestol pomade 5 %, Sandoz İlaç San. ve Tic. A.Ş., İstanbul, Turkey) was rubbed on the ear. To prevent eye dryness during anesthesia, Viscotears® eye pomade was rubbed on the eyes.

2.3. Reflex times

In order to evaluate the duration of anesthesia, the response times of the righting reflex (display of self-righting after the rabbit is laid dorso-ventrally), ear-pinch reflex (vocalization or moving head when the researcher pinches the auricle with two fingers) and pedal withdrawal reflex (withdrawal of hind leg when the researcher pinches one of the hind toes with hemostatic forceps) were used [14]. These responses were measured approximately every 30 s until they were absent and then assessed at predetermined time points throughout the period of anesthesia (T0, T5, T10, T15, T30, T45, T60, T75, T90, T105, T120). The data were collected by staff that were unaware of the DK and XK groups that were used. At the end of the study, the rabbits were rehomed.

2.4. Hemodynamic parameters

A pulse oximeter (Nellcor® OxiMax®, Compatible Veterinary Lingual sensor, Medtronic, Minneapolis, MN, USA) measured SpO2 via a lingual probe, and the SpO2 values were recorded together with HR. By using a Bionet BM3 VET bed-side monitor (Bionet Inc., Seoul, Republic of Korea), the hemodynamic parameters (HR, RR, SpO2, systolic blood pressure (SBP), diastolic blood pressure (DBP) were recorded before anesthetic injection (T0) and at the min 5 (T5), 10 (T10), 15 (T15), 30 (T30), 45 (T45), 60 (T60), 75 (T75), 90 (T90), 105 (T105) and 120 (T120) of anesthesia. The mean arterial blood pressure (MAP) value was calculated with the formula MAP = [SBP + (2 X DBP)] / 3.

2.5. Blood gas and electrolyte values

A 20 G branule was inserted on each rabbit in the central ear artery (A. auricularis) and left in place during anesthesia. Blood samples were collected before the injection (T0) and at the min 5 (T5), 10 (T10), 15 (T15), 30 (T30), 60 (T60), 90 (T90) and 120 (T120) during anesthesia for analysis of blood gas and electrolyte. A 0.5 mL blood sample (Ayset®, 2 ml blood gas syringe containing dry lithium heparin) was taken for each analysis. From these samples, by using an Epoc Blood Analysis device (Epocal Inc., Ottawa, Canada) and a BGEM Test Card kit (Epocal Inc.), pH, pCO_2, pO_2, $cHCO_3$, Be(ecf), Na^+, K^+, Ca^+, Cl^-, $cTCO_2$, AGaPK, Hct, cHgb, BE(b), glucose, lactate and creatine values were measured [2,9,11]. To prevent stasis formation, a 0.9% NaCl solution was mixed with heparin sodium (Koparin®), and the branule was washed with some of the mixture after obtaining each sample.

2.6. Statistical analysis

The data on the measured values were analyzed by using a package software (SPSS 25.0, IBM Corp., Armonk, NY, USA). The significance of the intergroup differences based on the measured variables was tested by Mann-Whitney U test with a 5% margin of error.

In the characteristics with repeated measurements, the differences among the measurement values were analyzed separately for each group (DK and XK) with Friedman test as the data were not normally distributed. In the characteristics with significant differences, pairwise comparisons were carried out with Wilcoxon paired-samples test.

For the measured variables, the minimum, maximum and median values that were obtained from the material of this study before the implementation (0th min) were accepted as the normal values (reference values) of this study. The recovery time was assessed in reference to the baseline values for each variable. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Findings on the reflex values

While determining the anesthesia depths in the DK and XK groups, the righting reflex, ear-pinch reflex, pedal withdrawal reflex, jaw muscle tone and palpebral reflex were utilized. Table 1 shows the time-dependent median results of the DK and XK groups. There was no statistically significant difference between the DK and XK groups in terms of the righting reflex, ear-pinch reflex and pedal withdrawal reflex ($P > 0.05$). Both groups provided an anesthetically smooth and uncomplicated recovery.

Table 1. Time-dependent median results of reflex loss in eight rabbits receiving DK (Dexmedetomidine 25 µg/kg, Ketamine 30 mg/kg) and XK (Xylazine 4 mg/kg, Ketamine 30 mg/kg) via IM.

	Induction		Recovery	
	Time to loss (min)		Time to present (min)	
	DK	XK	DK	XK
Righting reflex	6.0	6.5	121.0	123.5
Ear-pinch reflex	4.5	7.0	102.5	96.5
Pedal withdrawal reflex	4.5	6.0	105.0	102.5

3.2. Findings on the hemodynamic parameters

The HR, RR, SBP, DBP, MAP and SpO2 values were measured as the hemodynamic parameters. Table 2 shows the time-dependent median results on the hemodynamic parameters.

The difference between the DK and XK groups in terms of HR was significant at the 5th, 10th and 15th min ($P < 0.05$) and insignificant at the other measurement times ($P > 0.05$). Accordingly, at the measurement times with significant differences, the DK group had significantly higher HR values than the XK group. In the intragroup assessment of the time-dependent change in HR, the DK group showed a decrease up to the 75th min from the time of anesthesia induction, and these values increased back towards normal HR values after the 75th min. The XK group showed a decrease up to the 15th min from the time of anesthesia induction, these values increased up to the 60th min, and they showed irregular changes after the 60th min.

The difference between the DK and XK groups in terms of RR was found statistically insignificant ($P > 0.05$). In the intragroup assessment of the time-dependent change in RR, the time-dependent change was insignificant in the XK group and significant in the DK group ($P < 0.05$). Accordingly, the DK group showed a dramatic decrease up to the 5th min from the time of anesthesia induction, it showed a mild increase at the 10th min, there was a reduction again at the 15th min, and the values increased from the 15th min to the 105th min.

The difference between the DK and XK groups in terms of SBP and DBP was statistically insignificant ($P > 0.05$). In the intragroup assessment of the time-dependent change in DBP, in both the DK and XK groups, the DBP value obtained before anesthetic injection was found to be significantly higher than the values obtained throughout the anesthesia process (T0, T5, T10, T15, T30, T45, T60, T75, T90, T105, T120) ($P < 0.05$).

The difference between the DK and XK groups in terms of SpO_2 was found to be significant only at the 120th min ($P < 0.05$). In the intragroup comparisons, while the SpO2 value decreased up to the 10th min from the moment of anesthesia induction in the DK group, it increased from the 10th min on, and it reached the initial values at the 120th min. In the XK group, the SpO2 value decreased from the moment of anesthesia induction up to the 10th min, it gradually increased from the 15th min on, and it reached the initial level at the 120th min.

3.3. Findings on the blood gas and electrolyte values

In the study, for the arterial blood gas and electrolyte findings, pH, pCO_2, PO_2, $cHCO_3$, BE (ecf), Na^+, K^+, $Ca^{+,}$ Cl^-, $cTCO_2$, AGaPK, Hct, cHgb, BE(b), glucose, lactate and creatine values were measured. Table 3 shows the time-dependent median results on the blood gas and glucose values [$cHCO_3$, BE (ecf), Na^+, K^+, Ca^+, Cl^-, $cTCO_2$, AGaPK, Hct, cHgb, BE(b), lactate and creatine values are not shown in the Table 3].

The difference between the DK and XK groups was insignificant in terms of pH ($P > 0.05$). While the differences in the DK group among the measurement times in terms of pH were insignificant ($P > 0.05$), the pH values in the XK group measured at the beginning and after the 60th min were significantly higher than those measured between the 5th min and 60th min ($P < 0.05$). In general, the pH values decreased up to the 15th min in both groups and increased after this point.

The difference between the DK and XK groups was insignificant in terms of pCO_2 ($P > 0.05$). In both groups, the starting pCO_2 values were found to be significantly lower than those at all other measurements ($P < 0.05$). The highest pCO_2 value was observed at the 15th min in the DK group and 30th min in the XK group. The initial and 5th-min pCO_2 values in the XK group were significantly

Table 2. Time-dependent median results of hemodynamic parameter changes in eight rabbits who received DK (Dexmedetomidine 25 µg/kg, Ketamine 30 mg/kg) and -XK (Xylazine 4 mg/kg, Ketamine 30 mg/kg) by the IM route.

	HR (beats per min)		RR (breaths per min)		SAP (mm/hg)		DAP (mm/hg)		MAP (mm/hg)		SpO_2 (%)	
Time Points	DK	XK	DK	XK	DK	XK	DK	XK	DK	XK	DK	XK
T_0	276^{A}	246^{A}	77.5^{A}	67	92.5^{A}	89.5^{A}	66.5^{A}	68.5^{A}	75.2	75.5	96^{A}	97.5^{A}
T_5	265^{Ab}	220^{ABa}	49^{B}	54	71.5^{B}	72.5^{B}	54^{AB}	58.5^{B}	59.8	63.2	85^{B}	81.5^{C}
T_{10}	212^{Bb}	191^{Ca}	51.5^{B}	50.5	52.5^{C}	60.5^{C}	43^{B}	41.5^{C}	46.2	47.8	79^{B}	75^{CD}
T_{15}	209^{Bb}	175^{Ca}	42.5^{BC}	50.5	51^{C}	67^{C}	39^{B}	39.5^{C}	43.0	48.7	81^{B}	75.5^{CD}
T_{30}	195^{BC}	182^{C}	46^{BC}	50.5	51^{C}	65^{C}	36.5^{B}	43^{C}	41.3	50.3	85.5^{B}	85^{C}
T_{45}	189^{BC}	188.5^{C}	52^{B}	54	58.5^{C}	55.5^{C}	41^{B}	35.5^{C}	46.8	42.2	87^{B}	88^{C}
T_{60}	188^{C}	206.5^{C}	52.5^{B}	55	61.5^{C}	64.5^{C}	43^{B}	37^{C}	49.2	46.2	91^{AB}	89.5^{ABC}
T_{75}	184.5^{BC}	191.5^{C}	52^{B}	59.5	59^{C}	58^{C}	42.5^{B}	45.5^{C}	48.0	49.7	93^{A}	92.5^{A}
T_{90}	190.5^{BC}	183^{C}	55^{B}	61	60.5^{C}	62.5^{C}	43^{B}	36.5^{C}	48.8	45.2	91.5^{AB}	93^{AB}
T_{105}	211^{BC}	197^{C}	61.5^{B}	63	59.5^{C}	59^{C}	46.5^{B}	37.5^{C}	50.8	44.7	93.5^{A}	95^{A}
T_{120}	221^{B}	195.5^{C}	59^{B}	62	68.5^{BC}	61.5^{C}	50.5^{B}	41^{C}	56.5	47.8	94^{Ab}	98^{Aa}

T_0 = Preinjection, baseline, $T_{5, 10, 15, 30, 45, 60, 75, 90, 105, 120}$ = Min after T_0. HR = Heart rate, RR = Respiratory rate, SAP = Systolic arterial pressure, DAP = Diastolic arterial pressure, MAP = Mean arterial blood pressure, SpO2 = Arterial hemoglobin oxygen saturation.
A, B, C: The difference among the median values that are shown with different letters in the same column is statistically significant ($P < 0.05$).
a, b: The difference among the median values that are shown with different letters in the same line is statistically significant ($P < 0.05$).

lower than all other measurement values ($P < 0.05$). The differences among the 10th-min and later measurements were found to be insignificant ($P > 0.05$).

The difference between the DK and XK groups was insignificant in terms of pO_2 ($P > 0.05$). The initial measurement value in the DK group was higher than all other measurements. The differences among the other measurement times were insignificant ($P > 0.05$).

In terms of glucose, the difference between the DK and XK groups was significant at the 5th min ($P = 0.021$) ($P < 0.05$) and insignificant at the other measurements ($P > 0.05$). In the intergroup comparison of DK based on time, the initial and 15th-min glucose values were significantly lower than all others ($P < 0.05$), while the glucose values at the 60th and 90th min were significantly higher than all others ($P < 0.05$). In the intragroup comparison of XK based on time, the glucose value at the 5th min was significantly lower than all others ($P < 0.05$). While the initial, 10th-min and 15th-min glucose values were significantly higher than that at the 5th min ($P < 0.05$), they were not significantly lower than those at the 30th min and later ($P > 0.05$).

The difference between the DK and XK groups was insignificant in terms of their $cHCO_3$, BE (ecf), Na^+, K^+, Ca^+, Cl^-, $cTCO_2$, AGaPK, Hct, cHgb, BE(b), lactate and creatine values ($P > 0.05$).

4. Discussion

Studies are going on with different anesthesia protocols for creation of ideal anesthesia combinations in veterinary anesthetics. As the mortality rate is high in the anesthesia of rabbits, doses that are accepted as reliable and safe need to be used [3,9,11,15]. The literature has described different α2 adrenergic agonists in rabbits by themselves and in combination with ketamine at different doses [8,9,11–14,16]. In this study, the dose selection was made according to the pilot studies (DK combination; Bellini et al. [3], Bienert et al. [12], Nishida et al. [16], Zornow et al. [17], XK combination; Henke et al. [9], Kılıç [11]), in which the duration of anesthesia was determined according to the reflex values of the rabbits without surgery. For this reason, this study applied single IM injections of the DK combination at doses (dexmedetomidine 25 µg/kg and ketamine 30 mg/kg) recommended by Bellini et al. [3], Bienert et al. [12], Nishida et al. [16] and Zornow et al. [17] and the XK combination at doses (xylazine 4 mg/kg and ketamine 30 mg/kg) recommended by Henke et al. [9], Kılıç [11] and Difilipo et al. [14]. With the hope of determining a protocol with a better cardiovascular profile, the effects of these combinations on reflex findings, anesthesia duration and hemodynamic and hematological parameters in rabbits were examined.

The data in the literature have defined the onset of anesthesia as the loss of the righting reflex, ear-pinch

Table 3. Time-dependent median results of blood gas and electrolyte changes in eight rabbits receiving DK (Dexmedetomidine 25 µg/kg, Ketamine 30 mg/kg) and -XK (Xylazine 4 mg/kg, Ketamine 30 mg/kg) by the IM route

	pHa		pCO_2 (mmHg)		pO_2 (mmHg)		Glu (mg/dL)	
Time Points	DK	XK	DK	XK	DK	XK	DK	XK
T_0	7.46	7.42^{A}	28.05^{A}	28.15^{A}	155.15^{A}	124.05	213^{A}	206^{B}
T_5	7.35	7.37^{C}	35.25^{B}	28.35^{A}	68.4^{B}	88	258^{Bb}	174^{Aa}
T_{10}	7.35	7.36^{C}	40.95^{B}	36.7^{C}	60.95^{B}	78.7	254^{B}	209.5^{B}
T_{15}	7.35	7.35^{C}	44.75^{B}	40.75^{C}	76.3^{B}	60.95	220.5^{A}	219^{B}
T_{30}	7.38	7.38^{C}	37.15^{B}	44.55^{C}	86.65^{B}	91.75	246^{B}	253^{C}
T_{60}	7.42	7.42^{A}	40.15^{B}	39.9^{C}	73.35^{B}	63.1	275^{C}	289^{C}
T_{90}	7.47	7.44^{AB}	37.4^{B}	38.4^{C}	89^{B}	79.95	297.5^{C}	272^{C}
T_{120}	7.46	7.45^{AB}	38.95^{B}	38.55^{C}	91.6^{B}	85.5	256^{B}	275^{C}

T_0 = Preinjection, baseline, $T_{5, 10, 15, 30, 60, 90, 120}$ = Min after T_0. pHa = Arterial pH, pCO_2 = Partial pressure of carbon dioxide in arterial blood (mmHg), pO_2 = Partial pressure of oxygen in arterial blood (mmHg), Glu = Glucose(mg/dL).

A, B, C: The difference among the median values that are shown with different letters in the same column is statistically significant ($P < 0.05$).

a, b: The difference among the median values that are shown with different letters in the same line is statistically significant ($P < 0.05$).

reflex and pedal withdrawal reflex, while recovery has been defined as the return of all these reflexes [4,8–10,12,14]. No surgery was applied in this study. The surgical anesthesia duration was tested as reported in the literature by assessment of the righting reflex, ear-pinch reflex and pedal withdrawal reflex. The mean time of surgical anesthesia was determined as 115 min in the DK group and 116.5 min in the XK group. Both groups allowed recoveries at similar times. Bienert et al. [12] reported that, in adult rabbits, reflex loss and return times varied based on the dose of dexmedetomidine, and high doses provided longer sedation durations and longer return times of the pedal withdrawal reflex. In the study where only dexmedetomidine was administered (35 µg/kg, intravenous), the time of loss of the pedal withdrawal reflex and the time of return of the pedal withdrawal reflex were shorter in comparison to our findings. In the study by Karasu et al. [8], the xylazine (5 mg/kg)-ketamin (50 mg/kg) combination caused the loss of the righting reflex in a shorter time than that in our study. In our study, the difference in the times of loss and return of the pedal withdrawal reflex compared to the study carried out by Bienert et al. [12] was considered to have been caused by the difference in the administration route (IM) of dexmedetomidine and the combined use of ketamine with dexmedetomidine. Additionally, according to the study conducted by Karasu et al. [8], the longer loss of the righting reflex was considered to have been associated with the lower dose of ketamine usage (30 mg/kg) in the XK group.

The quality of recovery from anesthesia was assessed by the presence of excitation, muscle vibrations and sound-making after the return of the righting reflex [4]. The finding that excitation, muscle vibrations and sound-making were not encountered at the recovery stage suggested that the doses used in both groups provided suitable anesthesia.

It was reported that α2 agonists cause noticeably bradycardia in rabbits [9,10,18]. Bienert et al. [12] emphasized that dexmedetomidine caused bradycardia without depending on the dosage. In their study where different doses of dexmedetomidine were used, Ren et al. [13] stated that dexmedetomidine may lead to bradycardia in a dose-dependent manner. Karasu et al. [8] reported that the xylazine-ketamine combination led to bradycardia for 120 min. Baumgartner et al. [19] reported that, in rabbits, the xylazine-ketamine combination led to a reduction in HR, while ketamine by itself led to a tendency towards increasing HR. Hellebrekers et al. [4] stated that, application of the α2 adrenoceptor agonist medetomidine in rabbits significantly reduced HR at the beginning, while administration of ketamine at the 15th min significantly increased the HR. In this study, the reduction in HR was noticeable in both groups, while it was lesser in the XK group. The bradycardia observed in the two groups was in parallel to the findings of other researchers [4,8–

10,12,13,18,19]. This situation could be explained by that initial administration of α2 agonists causes an increase in the arterial blood pressure by leading to peripheral vasoconstriction, and the increased vagal tone results in bradycardia [20].

In rabbits injected with dexmedetomidine-midazolam, Bellini et al. [3] emphasized that RR decreased up to the 45th min, and the mean RR was lower in the dexmedetomidine group. Nishida et al. [16] observed that dexmedetomidine in a low dose interval (1–30 μg/kg) showed a tendency to reduce RR. According to Karasu et al. [8], the xylazine-ketamine combination reduced RR in rabbits, RR was at the lowest value at the 30th min, and it showed an increase afterwards. Henke et al. [9] found that α2 adrenergic agonists medetomidine-ketamine and xylazine-ketamine combinations severely reduced RR, and hypoxemia was prevented by O2 supplementation. In agreement with the literature, this study determined a reduction in both groups in terms of RR [3,8,9,16]. In the DK group, there was a dramatic decrease in the first 15 min ($P < 0.05$), and the mean RR continued to be lower in comparison to the XK group throughout the 120 min. The increase in the mean RR in the DK group after falling up to the 15th min and in the XK group after falling up to the 30th min suggested that this could have been caused by the effect of ketamine or that the sedation effect of the α2 adrenergic agonists started wearing off. It was determined that oxygen supplementation was required for prevention of hypoxemia due to the reduced RR in both groups, more noticeably in the DK group.

Canpolat et al. [21] reported that, in the dexmedetomidine-ketamine-morphine combination, the SpO2 value decreased in comparison to the initial level in the first 20 min of anesthesia, and it started to increase by the 25th min. Orr et al. [10] stated in their study on rabbits that were given anesthesia by different doses of the combination of medetomidine-ketamine that the SpO2 values were generally low due to peripheral vasoconstriction, and the area selected for placing the probe affected the SpO2 values. The SpO2 findings obtained in this study by placing the probe into the tongue were in agreement with those reported by Canpolat et al. [21] and Orr et al. [10]. The SpO2 values before anesthesia and until the 120th min of anesthesia were found to be in the reference range reported by Eatwell et al. [22].

In terms of the arterial blood pH value, in the DK and XK groups, the initial pH value and all those obtained for 120 min were within the reference ranges [22–24]. It was observed that the findings on pH in both the DK and XK groups were in agreement with the information in the literature from studies working with α2 adrenoceptor agonist and ketamine combinations [2,9,11].

In terms of pCO_2 (mmHg) in the arterial blood, in the DK and XK groups, the initial pCO_2 values and all those obtained for 120 min were in the reference ranges reported by Ardiaca et al. [23] and Gallego [24], while the data at the 10th and 15th min in the DK group were slightly higher than the reference range reported by Eatwell et al. [22]. The findings obtained in this study were in agreement with the literature [9,11,21].

In terms of pO_2 (mmHg) in the arterial blood, in the DK and XK groups, the initial values and all those obtained for 120 min were in agreement with the reference range reported by Eatwell et al. [22], while they were higher than those reported by Gallego [24]. The data were in agreement with the findings of Henke et al. [9] and Kılıç [11], while they were different to those obtained by Weiland et al. [25]. It was considered that the difference may have been caused by Weiland et al.'s [25] method of using medetomidine, which is an α2 adrenoceptor agonist.

Consequently, it was observed that administration of the dexmedetomidine (25 μg/kg)-ketamine (30 mg/kg) and xylazine (4 mg/kg)-ketamine (30 mg/kg) combinations in healthy adult rabbits provided similar effects in terms of the reflex findings, anesthesia duration and hemodynamic and hematological parameters. There were no side effects related to the quality of recovery in either group. It was also concluded that, oxygen supplementation beginning with the induction of anesthesia is necessary to prevent hypoxemia due to reduced RR in the combination of α2 adrenergic agonists and ketamine, and the dexmedetomidine-ketamine combination should be used with care in patients with respiratory depression.

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