Rabbits are commonly anaesthetised both for experimental research and in clinical veterinary practice (31, 33). The high surface area/volume ratio of rabbits, their relatively small size, high metabolic rate, high stress levels and difficult control of their airways increase their risk of anaesthesia-related death (24, 33). While the risk of anaesthesia- and sedation-related death was reported as 0.17% in dogs and 0.24% in cats, it amounted to 1.39% in rabbits (6). Even holding rabbits may lead to intense stress and injuries (5). Alternative anaesthetic techniques are being studied to overcome various problems in rabbit anaesthesia and achieve safe and effective anaesthesia (27).

The use of ketamine-based combinations in rabbit anaesthesia, which started in the 1970s, still continues due to their ease of application, the relative safety of ketamine and its low cost (7, 12, 13, 27, 34). Ketamine is usually combined with α2-agonists, benzodiazepines or phenothiazines (7, 14). Especially xylazine/ketamine was very commonly used in the past (18). Due to its inadequate analgesic properties and negative effects on the respiratory and cardiovascular systems, xylazine has been replaced by agents with high α2-receptor affinity (medetomidine, dexmedetomidine) that have higher analgesic and sedative-hypnotic properties.
Dexmedetomidine, which is a dextrorotatory enantiomer of medetomidine, is a highly selective α2 agonist. In terms of anaesthetic activity, it is twice as strong as medetomidine and 40 times as strong as xylazine (30, 32). In veterinary medicine, it was reported that predictable, fast and smooth anaesthesia induction and sustainability are achieved with the dexmedetomidine-ketamine combination (1, 32).

Midazolam, which has an intense calming effect and produces good muscle relaxation in rabbits, is a benzodiazepine derivative. Due to its water-solubility, it may be used together with ketamine in the same syringe, and it has a twice as potent effect as diazepam (18, 25, 30). It was reported that benzodiazepine-ketamine combinations produce good muscle relaxation and analgesia and lead to less cardiopulmonary depression (14, 18).

One of the complications most frequently seen in small mammals during anaesthesia is respiratory depression. It was noted that the anaesthetic dose required to induce surgical anaesthesia is very close to the one that may cause respiratory arrest (18). To achieve the desired effect in terms of specificity and affinity in anaesthesia processes where α2 agonists are used, while the dose of the α2 agonist is being reduced, unrelated side effects should be minimised (8).

This study aimed to investigate the effects of a combination of low-dose ketamine (20 mg/kg) and high-dose dexmedetomidine (50 µg/kg) and a combination of midazolam (0.6 mg/kg) and ketamine (20 mg/kg) on reflexes, haemodynamic values and blood gas levels.

Material and method

Animals. The study used 16 male New Zealand rabbits aged 11-12 months and weighing between 3500 and 4500 g. Ten days before the experiment, the rabbits were kept in a group in a room with dust-free wood shavings on the ground and provided with commercial pellet feed (Nükleen® rabbit feed, İvedik/Ankara/Turkey) and ad libitum water. The temperature in the room was maintained at 20 ± 2°C, and humidity was 50-60%. By turning the room lighting on at 7 am and off at 7 pm, a 12-hour light/dark cycle was kept. The room humidity was 50-60%. By turning the room lighting on at 7 am and off at 7 pm, a 12-hour light/dark cycle was kept. The animals were not fasted before anaesthesia.

The study was conducted at the Animal Experiments Application and Research Center (HDAM) with approval no. 2018/002/04 granted by the Harran University Animal Experiments Local Ethics Board (HRÜ-HADYEK) on Feb. 26, 2018.

Instrumentation. Before the experiments, the rabbits were weighed on a precision scale and given clinical examinations. Only clinically healthy rabbits were included in the study. Hair over the central auricular artery (A. auricularis) was shaved. After antisepsis, a 26 G branule (Beybi®, Ümraniye/Istanbul/Turkey) was inserted into the A. auricularis. After placing a three-way stopcock to obtain repeated blood gas samples and continuously record blood pressure, an arterial line was connected to a previously calibrated arterial blood pressure transducer. For ECG monitoring, alligator clip electrodes were applied to the skin in the medial region of the upper part of the forelegs and the left hind leg of each rabbit. Oxy-haemoglobin saturation (SpO2) was measured using a pulse oximeter with clips placed onto the ear. Body temperature (BT) was monitored with a rectal probe. With regard to haemodynamic parameters, the heart rate (HR), mean arterial pressure (MAP), respiratory rate (RR), SpO2, end-tidal CO2 (EtCO2) and BT values were monitored with a Mindray UMEC12VET (Mindray UMEC12VET, Shenzen Mindray Bio-Medical Electronics Co, Shenzhen, China). The arterial pH, partial pressure of carbon dioxide in arterial blood (pCO2) and partial pressure of oxygen in arterial blood (pO2) were measured with an Epoc Blood Analysis device (Epocal Inc, Ottawa, Canada) and a BGM Test Card kit (Epocal Inc, Ottawa, Canada). In order to prevent stasis, after each sample collection process, the branule was washed with 0.4 ml of a mixture obtained by mixing heparin sodium (Koparin®, 25000 IU/5 ml I.V. Koçak Farma, İstanbul, Turkey) into a 0.9% NaCl (Polifileks® 500 ml, Tekirdağ, Turkey) solution.

Anaesthesia. In order to minimise stress, the animals were handled daily for one week before the experiments. For the standardization of the experiment, the injections and their monitoring processes were carried out between 9 am and 11 am in all rabbits. The rabbits were randomly divided into 2 groups (n = 8 per group): the DXK and MKD groups. The rabbits in DXK were given dexmedetomidine (50 µg/kg) (Dekstomid® flip top vials 200 mcg/2 ml, Polifarma İlaç, Ergene/Tekirdağ) and ketamine (20 mg/kg) (Alfamine%10® injection, Alfasan International B.V., Woerden/Netherlands), and the rabbits in MKD were given midazolam (0.6 mg/kg) (Zolamid® 15 mg/3 ml, Vem İlaç, Çankaya/Ankara) and ketamine (20 mg/kg) (Alfamine 10%® injection, Alfasan International B.V., Woerden/Netherlands). The drug combinations were mixed in the same syringe and injected by the same IM route into M. quadriceps femoris.

Reflex times. Anaesthesia depth was assessed by recording the loss and return times of the righting reflex (the rabbit showing righting by itself after being laid dorso-ventrally), pedal withdrawal reflex (the rabbit withdrawing its hind leg when one of its toes is pinched by the researcher with fingers) and ear-pinch reflex (vocalisation or moving head when the researcher pinches the pinna with two fingers). The moment at which all these reflexes disappeared was recorded as anaesthesia onset, while the moment at which all of them returned was recorded as the end of the total sleep period. At the end of the study, the rabbits were re-homed.

Time schedule. The reflexes were monitored every 30 seconds before the injection of the anaesthetics (baseline) and right after the injection until all reflexes returned. The haemodynamic parameters (HR, MAP, RR, SpO2, EtCO2 and BT) were recorded before the injection of the anaesthetics and at minutes 5 (T5), 10 (T10), 15 (T15), 30 (T30), 60 (T60), 90 (T90), and 120 (T120) of the anaesthesia, and arterial blood samples were collected at the same time points for arterial pH and arterial blood gas values (pCO2, pO2).

Statistical analysis. Since the data did not satisfy the parametric test assumptions, differences between the treatment groups (DXK and MKD) in all quantitative characteristics were measured by the Mann-Whitney U test. Differences between measurements repeated at different times on the same subject were determined by the Freidman test.
Results and discussion

The time-based median results in the assessment of the anaesthesia depth of DXK and MDK are given in Table 1. The difference between the groups in terms of the time of loss and return of the righting reflex and ear-pinch reflex and the time of return of the pedal withdrawal reflex was statistically insignificant (p > 0.05). The difference between the groups was statistically significant only in terms of the time of loss of the pedal withdrawal reflex (2.0 min in DXK, 7.5 min in MDK) (p < 0.05). The total sleep duration was 109 min in DXK and 95 min in MDK.

The time-based median results for the haemodynamic parameters of the DXK and MDK groups are given in Table 2.

| Tab. 1. Time-dependent median results of reflex loss in eight rabbits receiving dexmedetomidine-ketamine (dexmedetomidine 50 µg/kg, ketamine 20 mg/kg) and midazolam-ketamine (midazolam 0.6 mg/kg, ketamine 20 mg/kg) via IM |
|---|---|---|---|---|---|---|---|
| Time to loss  | Recovery  |
| (minutes)  | (minutes)  |
| Induction  | DXK  | MDK  | DXK  | MDK  | DXK  | MDK  |
| Righting reflex  | 3.5  | 5.0  | 112.5  | 100.0  |
| Pedal withdrawal reflex  | 2.0a  | 7.5b  | 107.5  | 102.5  |
| Ear-pinch reflex  | 3.5  | 5.5  | 95.0  | 92.5  |

Explanations: a, b – differences between the median values that are shown with different letters in the same line are statistically significant (p < 0.05); a, b – difference between the median values that are shown with different letters in the same column are statistically significant (p < 0.05); # – differences between the median values that are shown with different letters in the same line are statistically significant (p < 0.05)

| Tab. 2. Time-dependent median results of hemodynamic parameter changes in eight rabbits who received dexmedetomidine-ketamine (dexmedetomidine 50 µg/kg, ketamine 20 mg/kg) and midazolam-ketamine (midazolam 0.6 mg/kg, ketamine 20 mg/kg) via IM |
|---|---|---|---|---|---|---|---|
| Time points  | HR  | MAP  | RR  | SpO₂  | ETCO₂  | BT  |
|  | (beats per minute)  | (mm/hg)  | (breaths per minute)  | (%)  | (%)  | (°C)  |
| DXK  | MDK  | DXK  | MDK  | DXK  | MDK  | DXK  | MDK  | DXK  | MDK  | DXK  | MDK  |
| T₀  | 203.5  | 219.5  | 114.3  | 117.3  | 139.5  | 158.0  | 90.0  | 93.0  | 29.0  | 28.0  | 39.5  | 39.4  |
| T₅  | 190.5  | 179.0  | 100.2  | 121.5  | 58.5  | 94.5  | 73.5  | 87.5  | 33.5  | 33.5  | 39.6  | 39.5  |
| T₁₀  | 156.0  | 156.5  | 79.9  | 113.4  | 49.0  | 81.5  | 73.5  | 81.0  | 35.0  | 38.0  | 39.8  | 39.0  |
| T₁₅  | 154.5  | 154.0  | 81.7  | 88.3  | 48.0  | 80.5  | 71.5  | 86.5  | 36.0  | 37.0  | 39.8  | 39.1  |
| T₂₀  | 144.0  | 178.0  | 77.9  | 87.0  | 55.0  | 95.5  | 87.5  | 85.0  | 39.0  | 36.0  | 39.7  | 39.1  |
| T₂₅  | 134.0  | 184.5  | 70.4  | 99.0  | 50.0  | 104.5  | 92.0  | 89.5  | 39.0  | 31.0  | 38.9  | 38.5  |
| T₃₀  | 159.5  | 206.0  | 81.0  | 98.8  | 65.0  | 92.0  | 94.0  | 95.0  | 35.0  | 32.0  | 38.6  | 38.3  |
| T₆₀  | 199.0  | 212.0  | 72.5  | 100.7  | 57.5  | 126.0  | 96.5  | 96.5  | 35.5  | 32.0  | 38.9  | 38.2  |

Explanations: T₀ – pre-injection, baseline; T₅, T₁₀, T₁₅, T₂₀, T₂₅, T₃₀, T₆₀, T₉₀, T₁₂₀ – minutes after T₀; HR – heart rate; MAP – mean arterial pressure; RR – respiratory rate; SpO₂ – oxy-haemoglobin saturation; ETCO₂ – end-tidal CO₂; BT – body temperature; # – differences between the median values that are shown with different letters in the same column are statistically significant (p < 0.05); a, b – difference between the median values that are shown with different letters in the same line are statistically significant (p < 0.05)
of dexmedetomidine (50 µg/kg) was selected based on studies by Bellini et al. (3), Nishida et al. (26) and Ren et al. (28), the dose for midazolam (0.6 mg/kg) was selected based on Bellini et al. (3) and Dupras et al. (10), and the dose for ketamine (20 mg/kg) was selected based on Dupras et al. (10), Grint et al. (13), Hedenqvist et al. (15) and Orr et al. (27). Anaesthetic effects produced by dexmedetomidine at a dose of 25 µg/kg and ketamine at 30 mg/kg by single IM injection in rabbits were previously reported (21). In this study, to determine the effects of dexmedetomidine on respiration, a higher dose was used. The aim was also to examine these effects alongside changes caused by midazolam, which is known to have lesser cardiopulmonary effects. For this purpose, this study investigated the effects of a combination of low-dose ketamine (20 mg/kg) and high-dose dexmedetomidine (50 µg/kg) and a combination of midazolam (0.6 mg/kg) and ketamine (20 mg/kg) on reflexes, haemodynamic values and blood gas levels.

Since surgery was not performed in this study, the depth of surgical anaesthesia was evaluated according to the loss of the right reflex, pedal withdrawal reflex and ear-pinch reflex. At the doses studied, it was observed that, compared to midazolam-ketamine, dexmedetomidine-ketamine induced anaesthesia faster and the total sleep lasted longer. In the study by Kirazoglu et al., a lower dose of dexmedetomidine (25 µg/kg) took longer to induce anaesthesia (21). Another study reported that low doses of dexmedetomidine caused anaesthesia after a longer time, and at higher doses of dexmedetomidine, sedation lasted longer and more time was required for the return of the pedal withdrawal reflex (4). A study on rabbits conducted with medetomidine, which is an α2 agonist, found that the onset of anaesthesia with medetomidine-ketamine was faster than with midazolam-ketamine (13). Two studies conducted with a combination of midazolam (0.2 mg/kg) and ketamine (30 mg/kg) in rabbits reported shorter anaesthesia duration than our study (3, 10). The reflex times obtained in this study were compatible with findings of the researchers cited above (3, 13, 21). This was attributed to the fact that high-dose dexmedetomidine causes longer sedation and more time is required for the pedal withdrawal reflex to return (4), and high-dose midazolam leads to strong sedation (11). In most rabbits of both groups, chewing movements were observed as an indicator of recovery. It was thought that this resulted from ketamine injection, as reported by Henke et al. (18).

It is known that α2 agonists lead to a noticeable decrease in HR (7, 15, 18). In addition, it was reported that medetomidine and dexmedetomidine lead to bradycardia irrespective of the route of administration and dose (4, 27). On the other hand, it is known that the effect of midazolam at therapeutic doses on the cardiovascular system is minimal (3, 14, 18). It was demonstrated in rabbits that a greater decrease in

Tab. 3. Time-dependent median results of blood gas changes in eight rabbits receiving dexmedetomidine-ketamine (dexmedetomidine 50 µg/kg, ketamine 20 mg/kg) and midazolam-ketamine (midazolam 0.6 mg/kg, ketamine 20 mg/kg) by the IM route

| Time points | DXK pHa | DXK pCO2 (mmHg) | DXK pO2 (mmHg) | MDK pHa | MDK pCO2 (mmHg) | MDK pO2 (mmHg) |
|-------------|---------|----------------|----------------|---------|----------------|----------------|
| T0          | 7.46    | 21.80          | 93.40*         | 7.38    | 23.05*         | 92.20*         |
| T5          | 7.39    | 30.75*         | 89.10           | 7.44    | 25.25          | 95.80           |
| T10         | 7.40    | 36.20*         | 89.10           | 7.47    | 35.70*         | 97.95           |
| T15         | 7.41    | 37.55*         | 89.10           | 7.47    | 37.55*         | 91.40           |
| T60         | 7.54*   | 29.25*         | 89.10           | 7.55    | 29.25*         | 111.70          |
| T90         | 7.54*   | 29.25*         | 89.10           | 7.55    | 29.25*         | 111.70          |

Explanations: T0 – pre-injection, baseline; T5, 10, 15, 30, 60, 90, 120 – minutes after T0; pHa – arterial pH; pCO2 – partial pressure of carbon dioxide in arterial blood (mmHg); pO2 – partial pressure of oxygen in arterial blood (mmHg); # – differences between the median values that are shown with different letters in the same column are statistically significant (p < 0.05); a, b – difference between the median values that are shown with different letters in the same line are statistically significant (p < 0.05)

38.9°C, MDK: 38.2°C) (p < 0.05). BT was lower in MDK than it was in DXK throughout anaesthesia.

The time-based median results for the arterial blood gas parameters in DXK and MDK are shown in Table 3.

The difference between DXK and MDK in terms of the arterial pH was insignificant at all time points (p > 0.05). The pH decreased suddenly in both groups from the baseline to T10 in DXK (7.38 pH, MDK: pH 7.43) (p > 0.05) and remained at this level until T30 from the injection to T10 (p > 0.05). It was observed that pCO2 increased from its baseline values was examined, it was noticed that there was a dramatic decrease in both groups from the injection to T10 (DXK: 49.50 mmHg, MDK: 78.80 mmHg). The values in both groups started to increase after T10 and reached baseline levels at T30 (DXK: 103.40 mmHg, MDK: 111.70 mmHg). MDK showed a smaller decrease in pO2.

The literature recommends different doses for ketamine (15 to 50 mg/kg), and cardiopulmonary and reflex values were examined at these doses (10, 13, 15, 20, 27). In this study, the dose
HR was produced by dexmedetomidine, compared to midazolam, and by a medetomidine-ketamine combination, compared to a midazolam-ketamine combination (9, 13). In this study, in agreement with findings of other researchers (7, 9, 13, 15, 18), at the same ketamine dose, the combination of dexmedetomidine and ketamine depressed HR more and for a longer period, whereas in the midazolam-ketamine group of animals HR decreased during the first 15 min and then recovered. As ketamine has a positive chronotropic effect and stimulates the cardiovascular system (20), it was thought that keeping the ketamine dose low led to a longer-lasting bradycardia, especially with dexmedetomidine.

Many researchers emphasise that the combination of ketamine with α2 agonists reduces MAP (18, 20, 21). Cheng Chang et al. (9) reported that dexmedetomidine reduced MAP in rabbits and produced more hypotension than midazolam did. Bienert et al. (4) reported that dexmedetomidine changed MAP in a dose-dependent manner, and low-dose dexmedetomidine led to a higher reduction in MAP. They observed a relationship in which an increase of 10 µg/kg in the dose of dexmedetomidine led to an increase of 10.3 mmHg in MAP. Kirazoğlu et al. (21) found that the combination of dexmedetomidine (25 µg/kg) and ketamine (30 mg/kg) caused a significant reduction in MAP in rabbits. The relationship proposed by Bienert et al. (4) was not entirely compatible with MAP findings from the study by Kirazoğlu et al. (21). It was observed, however, that the dexmedetomidine-ketamine combination led to a significant decrease in MAP. MAP values decreased in both groups, but the decrease was more noticeable in DXK.

Although the doses and administration methods in previous studies were different, it is worth noting that α2 agonists reduced RR and caused hypoxemia in those studies (18, 20, 21, 27, 30). Kirazoğlu et al. (21) emphasised that the dexmedetomidine (25 µg/kg) and ketamine (30 mg/kg) combination they used led to a significant decrease in RR in rabbits. While it was reported that increasing the dose of medetomidine had a small effect on respiratory and cardiovascular depression (27), it was similarly observed that high-dose dexmedetomidine (50 µg/kg) did not depress ventilation as much as low-dose dexmedetomidine did (26). In this study, in agreement with findings of other researchers, the depressive effect on RR was more noticeable throughout anaesthesia in the DXK group, and the values were significantly lower than those in the MDK group (p < 0.05). In this study, in contrast to one by Kirazoğlu et al. (21), the RR values were similar at the specified time points during anaesthesia induced by dexmedetomidine at a dose increased to 50 µg/kg and ketamine at a dose reduced to 20 mg/kg, and as mentioned by Nishida et al. (26), high-dose dexmedetomidine (50 µg/kg) did not depress RR at the same rate as the low dose of the same substance did.

Although the groups were different, it was thought that this reduction in RR could have been a consequence of a reduction in the pulmonary blood perfusion rate and the direct effects of these drugs on the respiratory system.

Nishida et al. (26) emphasise that an increase in inspiratory CO2 concentration led to a decrease in RR in dexmedetomidine groups. Orr et al. (27) report that increasing the dose of medetomidine led only to an increase in end-tidal CO2 throughout anaesthesia and affected cardiovascular depression minimally. In the present study, the EtCO2 level in the DXK group increased as RR decreased, which was in agreement with results reported by Nishida et al. (26), but the same proportion of increase was not observed in the EtCO2 level in the MDK group. In the DXK group, as RR decreased, SpO2 decreased at the same proportion, and similarly, there was a decrease in SpO2 in parallel with the decrease in RR in the MDK group.

In both group, the decrease in RR right after the injection was accompanied by arterial blood gas changes. It has been emphasised that α2 agonist-ketamine combinations lead to hypoxia, hypercapnia and acidosis in rabbits, and that, when using these combinations, O2 supplementation is necessary (7, 16, 17, 20, 27, 29). It was reported that, although dexmedetomidine depressed ventilation, it did not lead to deep hypoxemia or hypercapnia (26), while the midazolam-ketamine combination may have caused moderate respiratory acidosis by leading to changes in blood gases, especially at the 30th and 60th minutes (2). In the present study, moderate hypoxia, hypercapnia and acidosis were found in DXK, whereas mild hypoxia, hypercapnia and acidosis occurred in MDK. In agreement with findings of other researchers except Nishida et al. (26), as a result of suppression of the respiratory system by the anaesthetics, these changes in both groups were noticeable especially within the first 15 min (2, 7, 10, 18, 20). This change may have been affected by the fact that the pO2 value at the baseline in DXK was significantly lower (p < 0.05), and O2 supplementation was provided in both groups at the end of the 120 min.

In this study, at the same dose of ketamine, dexmedetomidine led to significant changes in the haemodynamic values (greater decrease in HR and RR and low MAP) and blood gasses (greater decrease in pH and pO2, and increase in pCO2). The induction time was shortened by increasing the dexmedetomidine dose to 50 µg/kg and reducing the ketamine dose to 20 mg/kg, but at the specified time points, the RR values were close to those obtained with low-dose dexmedetomidine, and high-dose dexmedetomidine (50 µg/kg) did not depress RR at the same proportion to the dose.

Consequently, it was concluded that, in the New Zealand white rabbits, the midazolam (0.6 mg/kg) and ketamine (20 mg/kg) combination provided better profiles of haemodynamic and blood gas values, and
this combination could be considered appropriate for anaesthesia.

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