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Comparison of Clinical Effects of Propofol-Sevoflurane, Midazolam-Sevoflurane and Medetomidine-Ketamine-Sevoflurane Anesthesia in Rabbits

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Abstract
Objective: This study aimed to compare the clinical effects of propofol-sevoflurane (PS), midazolam-sevoflurane (MS), and medetomidine-ketamine-sevoflurane (MKS) anesthesia protocols in rabbits and to propose a safe and controlled alternative inhalation anesthesia technique using the endotracheal intubation method. **Materials and Methods:** The study was conducted on 30 white New Zealand rabbits (5 females and 5 males randomly selected per group) divided into three groups. In the PS group, propofol 7 mg/kg IV was administered; in the MS group, midazolam 0.3 mg/kg IM; and in the MKS group, medetomidine 0.3 mg/kg IM followed by ketamine 30 mg/kg IM. Subsequently, all groups received sevoflurane at 4% with 500 ml/kg/min oxygen. In all groups, anesthesia induction time, chewing reflex time (extubation time), righting reflex time, heart rate, respiratory rate, body temperature, and peripheral arterial hemoglobin saturation were determined. **Results:** During anesthesia, decreases in heart rate and body temperature were observed in all groups. Respiratory rate decreased during the first 30 minutes of anesthesia but increased again after the 45th minute. **Conclusion:** For both clinical and experimental procedures in rabbits, the propofol-sevoflurane combination is considered appropriate for less painful and short-term interventions, while the medetomidine-ketamine-sevoflurane combination is recommended for highly painful and long-term procedures.
Keywords: Rabbit, Anesthesia, Propofol, Midazolam, Sevoflurane.

Tavşanlarda Propofol-Sevofluran, Midazolam-Sevofluran ve Medetomidin-Ketamin-Sevofluran Anestezisinin Klinik Etkilerinin Karşılaştırılması

Öz
Amaç: Bu çalışmanın amacı, tavşanlarda propofol-sevofluran (PS), midazolam-sevofluran (MS) ve medetomidin-ketamin-sevofluran (MKS) anestezi protokollerinin tavşanlardaki klinik etkilerini karşılaştırmak ve tavşanlarda endotrakeal entübasyon tekniği ile güvenli ve kontrollü alternatif inhalasyon anestezisi tekniği önermektir. **Gereç ve Yöntem:** Çalışma, her bir grupta rastgele seçilen 5'i dişi, 5'i erkek 10 adet beyaz renkli Yeni Zelanda ırkı 30 adet tavşanda 3 grupta yapıldı. PS grubunda propofol 7 mg/kg IV, MS grubunda midazolam 0.3 mg/kg IM, MKS grubunda medetomidin 0.3 mg/kg IM ve ketamin 30 mg/kg IM uygulandı. Takiben tüm gruplarda tavşanlara sevofluran %4 olarak 500 ml/kg/dk oksijen ile uygulandı. Bütün gruplarda; anestezi indüksiyon süresi, çiğneme refleksi zamanı (ekstübasyon zamanı), doğrulma refleksi zamanı, dakikadaki kalp atım sayısı, solunum sayısı, vücut ısısı ve periferik arteriyel hemoglobin satürasyonu belirlendi. **Bulgular:** Çalışmadaki tüm gruplarda oluşan anestezi süresince kalp atım sayısı ve vücut ısısında düşüşler gözlendi. Solunum sayısında anestezinin ilk 30 dakikasında düşüşler gözlendi. Ancak, 45. dakikadan sonra tekrar yükseldi. **Sonuç:** Tavşanlarda yapılacak olan gerek deneysel gerekse klinik cerrahi uygulamalarda; az ağrılı ve kısa süreli girişimlerde propofol-sevofluran kombinasyonunun; çok ağrılı ve uzun süreli girişimlerde ise medetomidin-ketamin-sevofluran kombinasyonunun kullanılmasının uygun olacağı kanaatine varıldı.
Anahtar Kelimeler: Tavşan, Anestezi, Propofol, Midazolam, Sevofluran.

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INTRODUCTION

Rabbits are among the most suitable animal models for pharmacology, toxicology, surgery, and genetic research due to their advantageous characteristics, including docility, ease of handling, straightforward care and feeding requirements, and large ear veins (Cruz et al., 2010). Despite the availability of numerous safe anesthetic options for clinical procedures in rabbits, their mortality and morbidity rates remain higher compared to cats and dogs. This can be attributed primarily to species-specific physiological traits that render rabbits prone to respiratory depression, their small anatomical structures, the narrow margin between anesthetic and toxic doses, and their sensitivity to stress during the preoperative period (Borkowski & Karas, 1999).

While low-complication anesthesia protocols are commonly used for research purposes, clinical cases in rabbits are often associated with a high incidence of anesthesia-related complications and mortality. Contributing factors to this elevated mortality rate include the frequent use of short-term general anesthesia in scientific studies, the lack of species-specific anesthesia protocols, clinicians' limited familiarity with rabbits, and the poor health condition of rabbits presenting to clinics (Hall et al., 2001; Kim et al., 2004).

Both injectable and inhalation anesthetic methods are utilized for rabbits. While inhalation anesthetics are commonly used as the sole anesthetic in smaller guinea pigs, injectable agents are often combined with inhalation anesthesia in rabbits and larger guinea pigs. In rabbits, short-term general anesthesia can be safely administered with injectable anesthetic drugs, either alone or in combination with sedatives, tranquilizers, and analgesics. Anesthetic combinations, particularly xylazine/ketamine, were widely used in the past. However, research has demonstrated that these combinations often lack adequate analgesic properties for major surgical procedures and frequently cause significant hypotension, increasing the risk of mortality. Therefore, in cases where a combination of injectable anesthetic drugs and sedatives is necessary, each selected drug must fulfill one of the balanced anesthesia criteria: narcosis, analgesia, or muscle relaxation (Hall et al., 2001; Henke et al., 2005).

This study aims to compare the clinical effects of three anesthesia protocols: propofol-sevoflurane, midazolam-sevoflurane, and medetomidine-ketamine-sevoflurane in rabbits, and to recommend a safe and controlled alternative inhalation anesthesia technique using the endotracheal intubation.

MATERIALS AND METHODS

Study group

In this study, 30 New Zealand White rabbits (15 females and 15 males), aged 1–3 years and weighing 1.5–3 kg, were randomly divided into three groups, 10 each containing five females and five males.

Procedures

In the Propofol-Sevoflurane (PS) group, rabbits received propofol (Propofol 1% Fresenius, Fresenius Kabi, Germany) at 7 mg/kg intravenously, administered as half the dose rapidly and the remainder over 30 seconds, followed by sevoflurane (Sevoflurane, Baxter, Türkiye) at 4% with an oxygen flow rate of 500 ml/kg/min. In the Midazolam-Sevoflurane (MS) group, rabbits were administered midazolam (Demizolam, Delta Select GmbH, Germany) intramuscularly at 0.3 mg/kg, followed by sevoflurane at the same concentration and oxygen flow rate. In the Medetomidine-Ketamine-Sevoflurane (MKS) group, medetomidine (Domitor, Pfizer, Germany) at 0.3 mg/kg was given intramuscularly, followed by ketamine (Alfamine, Alfasan, Nederland) at 30 mg/kg three minutes later, and then sevoflurane as described for the other groups. In all groups, anesthesia was maintained for 30 minutes using an anesthesia machine (TMS, Maxi 2200, Türkiye) with a size 2.5 cuffed endotracheal tube and a Magill-type non-rebreathing circuit. The rabbits were disconnected from the device at the end of the 30 minutes.

Monitoring

In all groups, various parameters were evaluated to assess the effects of the anesthesia protocols. These included the anesthesia induction time, defined as the time from sevoflurane application until the rabbit lay on its side; the time to loss of response to pain and reflex tests; the chewing reflex time (extubating time), which measured the time from the cessation of sevoflurane until chewing movements resumed after 30 minutes of inhalation anesthesia; and the righting reflex time, representing the time required for the rabbit, placed on its back after discontinuation of sevoflurane, to stand on all four legs. The quality of anesthesia induction, surgical anesthesia, analgesia and emergence from anesthesia were subjectively evaluated by modified criteria from a previous study by Allweiler et al. (2010) with scores assigned as excellent (3 points), good (2 points), or poor (1 point) (Table 1). Pain and reflex tests—such as pricking, needle pricks, and pinching with toothed hemostatic forceps—were applied to the pinna and interdigital regions of the fore and hind legs every 10 minutes during the 30-minute anesthesia period and at 15, 30, 60, and 90 minutes after anesthesia to assess surgical anesthesia quality and duration. Intubation quality was similarly scored based on the number of attempts and time taken (<2 attempts and <2 minutes for good, <4 attempts and <5 minutes for mediocre, >4 attempts and >5 minutes for poor), using modified criteria from Allweiler et al. (2010). The number of attempts determined the intubation ease and whether direct visualization via an laryngoscope was required.

To evaluate the cardiopulmonary effects of the anesthetic combinations, cardiopulmonary parameters and body temperature were recorded before anesthesia,

every 10 minutes during the 30-minute anesthesia period, and at 15-, 30-, 60-, and 90-minute post-anesthesia. Heart rate was measured with a stethoscope, while the respiratory rate was determined by observing costo-abdominal movements and body temperature with a thermometer, and peripheral arterial hemoglobin oxygen saturation (SpO_2) was recorded using a pulse oximeter (G9000F, Cardel) with probe placed on the shaved tail root. Additional physiological changes and complications such as apnea, apneustic breathing, salivation, anorexia, and laryngospasm were also documented during the trials and up to 24 hours afterward.

Statistical analysis

The data were presented as mean ± standard deviation (Mean±SD). For analyzing cardiopulmonary parameters and body temperature, two-way analysis of variance (Two-Way ANOVA) was employed for intragroup (repeated measures) comparisons. In contrast, one-way analysis of variance (One-Way ANOVA) was used for intergroup comparisons at the same time points. The nonparametric Mann-Whitney U test was also applied to evaluate clinical anesthesia parameters. A p-value of ≤ 0.05 was considered statistically significant. Statistical analyses were conducted using the Minitab v.11.0 software.

Ethical considerations

The study was conducted with the approval of the Erciyes University Animal Experiments Local Ethics Committee (Date: 15.02.2017, Approval No: 17/019).

RESULTS

The anesthetic combinations of propofol-sevoflurane (Group I, PS), midazolam-sevoflurane (Group II, MS), and medetomidine-ketamine-sevoflurane (Group III, MKS), administered at the specified doses, were all effective in producing safe general anesthesia. The protocols provided relatively good muscle relaxation and analgesia without causing any mortality.

Table 1. Evaluation criteria for the quality of anesthesia induction, the quality of surgical anesthesia and analgesia, the quality of emergence, and ease of intubation.

Excellent=3 points	Good=2 points	Poor=1 points
Induction Quality		
He quickly came to sternal position or lay on his side. No excitation. Good muscle relaxation. No response to pain and reflex tests.	Induction prolonged. Mild excitation. Attempts to get up after lying on the side. Poor muscle relaxation. Mild response to pain and reflex tests.	Induction is too long. Marked excitation. Did not lie on the side. Weak muscle relaxation. Vocalized. Marked response to pain tests.
Quality of Surgical Anesthesia and Analgesia		
No response to pain and reflex stimuli.	Light response to pain and reflex stimuli. Slight head movement. Slight foot movement.	Clear response to pain stimuli. Clear movements entire the body. Chewing movements are present. The jaw tone is not completely lost.
Quality of Waking Up		
Recovery of the righting reflex is fast. Able to walk with slight ataxia.	Recovery of the righting reflex is slow. Ataxia is evident when standing and walking. Mild excitation.	Recovery of the righting reflex is very slow. Unable to stand. Struggling and flailing on the ground are significant and prolonged. Marked excitation.
Ease/Comfort of Intubation		
< 2 attempts, time < 2 minutes	< 4 attempts, time < 5 minutes	> 4 attempts, time > 5 minutes

The cardiopulmonary effects of Groups I, II and III are detailed in Table 2, while the clinical anesthesia effects are summarized in Table 3. Heart rate showed statistically significant decreases ($p<0.05$) compared to the initial value at all sampling times following anesthesia induction in all groups. When comparing heart rates between groups, Group III exhibited statistically significantly lower values ($p<0.05$) than Groups I and II across all sampling times.

In terms of respiratory rate, statistically significant decreases ($p<0.05$) were observed during the anesthesia period (10, 20, and 30 minutes) compared to the initial value in all groups. After the rabbits were disconnected from the anesthesia device, respiratory rate increased significantly ($p<0.05$) in all groups at subsequent sampling times. Between-group comparisons revealed that Group III had significantly lower respiratory rates ($p<0.05$) than Groups I and II at all sampling times. Additionally, while respiratory rates in Groups I and II exceeded their respective initial values at 60, 90, and 120 minutes, the respiratory rate in Group III remained below the initial value at these time points.

In all groups, statistically significant decreases in body temperature ($p<0.05$) were observed during the first 60 minutes of anesthesia compared to the initial values. However, body temperature increased after the 60th minute in all groups ($p<0.05$), though it remained lower than the initial values. Between-group comparisons showed that Group I exhibited statistically significantly lower body temperature values ($p<0.05$) than the other groups at the 10th, 20th, 30th, and 45th minutes. Despite increases in body temperature at the 60th, 90th, and 120th minutes in all groups, it remained below the initial (control) values, and the differences in body temperature between the groups at these later time points were statistically insignificant.

Peripheral arterial hemoglobin oxygen saturation (SpO_2) showed a statistically significant increase ($p<0.05$) compared to the initial values during the anesthesia period across all groups. After oxygen administration ceased and the rabbits were disconnected from the anesthesia device, SpO_2 values decreased in all groups compared to the initial values. At the 120th minute, SpO_2 in Groups I and II remained slightly below the initial value, while in Group III, it was higher than the initial (control) value. Group III exhibited significantly lower SpO_2 values ($p<0.05$) in between-group comparisons than the other groups, particularly at the 20th, 30th, 45th, and 60th minutes. However, the SpO_2 of Group III increased after the 45th minute, returning to levels comparable to the initial value by the 120th minute..

Table 2. Mean values of heart rate, respiratory rate, body temperature, pulse oximetry measurements and surgical anesthesia/analgesia quality of the groups (Mean±SD).

	Control	10. min	20. min	30. min	45. min[1]	60. min[2]	90. min[3]
Heart Rate (/min)							
Group I	310.3±15.7^{x,a}	279.9±32.1^{x,b}	267.9±29.6^{x,b}	262.0±31.9^{x,b}	231.1±25.4^{x,c}	231.0±19.8^{x,c}	217.1±29.7^{x,c}
Group II	308.8±18.9^{x,a}	262.7±38.3^{x,b}	252.7±38.4^{x,bc}	244.2±41.5^{x,bc}	233.7±29.2^{x,bc}	229.6±38.3^{x,bc}	221.4±49.6^{x,c}
Group III	299.5±11.8^{x,a}	200.2±13.6^{y,b}	193.1±15.2^{y,bc}	187.7±13.6^{y,bc}	178.7±21.3^{y,c}	174.3±19.5^{y,c}	168.1±17.3^{y,c}
Respiratory Rate (/min)							
Group I	68.4±19.8^{x,a}	37.6±7.4^{x,b}	38.0±7.4^{x,b}	39.4±6.8^{x,b}	60.4±22.8^{x,a}	84.0±22.4^{x,ac}	96.0±18.7 ^{x,c}
Group II	73.1±10.2^{x,a}	38.0±7.4^{xy,bc}	35.2±8.2^{x,b}	33.6±7.6^{x,b}	51.6±19.4^{x,c}	74.0±19.1 ^{xy,a}	82.4±17.1^{xy,ad}
Group III	68.2±11.3^{x,a}	27.2±14.9^{y,b}	23.2±11.4^{y,b}	23.6±10.4^{y,b}	48.0±12.1^{x,c}	56.8±10.8^{y,ac}	64.4±23.9 ^{y,ac}
Body Temperature (ºC)							
Group I	39.8±0.2 ^{x,a}	38.3±0.4 ^{x,b}	38.0±0.5 ^{x,bc}	37.6±0.5 ^{x,c}	37.4±0.6 ^{x,c}	37.7±0.9 ^{x,c}	38.2±0.5 ^{x,b}
Group II	39.8±0.2 ^{x,a}	38.7±0.6 ^{xy,b}	38.2±0.4 ^{y,b}	37.9±0.6 ^{y,c}	37.7±0.8 ^{xy,c}	37.7±0.6 ^{x,c}	38.1±0.9 ^{x,bc}
Group III	39.7±0.3 ^{x,a}	39.0±0.7 ^{y,b}	38.9±0.7 ^{y,bc}	38,8±0.7 ^{y,bc}	38.3±0.8 ^{y,c}	38,3±0.8 ^{x,c}	38.2±0.9 ^{x,c}
Peripheral Arterial Hemoglobin Oxygen Saturation (SpO_2) (%)							
Group I	96.9±1.5 ^{x,a}	98.6±0.5 ^{x,b}	98.6±0.7 ^{x,b}	98.6±0.7 ^{x,b}	97.7±1.1 ^{x,ab}	97.3±1.4 ^{x,ab}	97.3±1.8 ^{x,ab}
Group II	95.2±2.4 ^{xy,a}	98.2±1.1 ^{x,ab}	98.3±0.7 ^{xy,b}	98.6±1.0 ^{x,b}	96.1±3.0 ^{x,ab}	94.9±3.4 ^{xy,a}	94.3±3.2 ^{xy,a}
Group III	94.8±1.6 ^{y,a}	97.9±1.4 ^{x,b}	96.2±3.6 ^{y,ab}	96.0±4.6 ^{x,ab}	90.4±4.1 ^{y,c}	92.8±2.0 ^{y,ac}	95.7±1.8 ^{y,ab}
Surgical Anesthesia/Analgesia Quality*							
Group I	-	2.30±0.5 ^{x,a}	2.10±0.3 ^{x,ab}	1.90±0.3 ^{x,b}	1.90±0.3 ^{x,b}	1.50±0.5 ^{x,c}	1.10±0.3 ^{x,d}
Group II	-	2.20±0.4 ^{x,a}	2.10±0.3 ^{x,a}	1.9±0.3 ^{x,a}	1.9±0.3 ^{x,a}	1.40±0.5 ^{x,b}	1.10±0.3 ^{x,bc}
Group III	-	2.90±0.3 ^{y,a}	2.90±0.3 ^{y,a}	2.90±0.3 ^{y,a}	2.70±0.5 ^{y,ab}	2.30±0.7 ^{y,b}	1.4±0.5 ^{x,c}

The difference between means with different letters in the same row (a,b,c,d) and column (x,y) is statistically significant ($p<0.05$).
Group I: Propofol-Sevoflurane (PS), Group II: Midazolam-Sevoflurane (MS), Group III: Medetomidine-Ketamine-Sevoflurane (MKS).
[1] The 15th, [2] 30th and [3] 60th minute after 30 minutes of sevoflurane application.
* Evaluated according to the criteria in Table 1.

Surgical anesthesia and analgesia quality were significantly better ($p<0.05$) in Group III compared to Groups I and II. Still, no statistically significant differences were observed at the 90th and 120th minutes. Within-group comparisons showed a statistically significant decline in surgical anesthesia/analgesia quality over time in all groups. Group I had the shortest time for anesthesia induction, followed by Groups III and II, with statistically significant differences ($p<0.05$). Regarding anesthesia induction quality, Group II was significantly weak ($p<0.05$). Similarly, Group II showed significantly weaker ($p<0.05$) intubation ease than Groups I and III.

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Chewing reflex onset (extubation) time was significantly earlier ($p<0.05$) in Group I compared to the other groups. The righting reflex duration was considerably longer ($p<0.05$) in Group III than in Groups I and II. Arousal quality was significantly weaker ($p<0.05$) in Group III compared to the other groups. The mucous membrane color remained normal in all rabbits, with no signs of cyanosis observed during anesthesia. Furthermore, no significant complications occurred during or after anesthesia induction, such as apnea or apneustic breathing. No mortality or complications were observed during the 24-h post-anesthesia observation period.

Table 3. Mean clinical anesthesia evaluation parameters values for the groups (Mean±SD).

Parameter	Group I	Group II	Group III
Anesthesia induction time (min)	1.5±0.45 [x]	4.06±0.83 [y]	2.81±0.40 [z]
Anesthesia sedation/induction quality	2.2±0.52 [x]	1.50±0.52 [y]	2.70±0.48 [x]
Ease of intubation	2.10±0.56 [x]	1.10±0.31 [y]	2.70±0.48 [x]
Chewing reflex onset time (Extubating time) (min)	38,70±3.12 [x]	52.40±13.48 [xy]	65.20±20.64 [y]
Righting reflex time (min)	41.40±4.43 [x]	51.80±9.38 [x]	119.90±15.61 [y]
Awakening quality	2.90±0.31 [x]	2.60±0.51 [x]	1.30±0.48 [y]

DISCUSSION

Safe and effective rabbit anesthesia is crucial in experimental studies and clinical applications. Inhalation anesthesia is considered the safest method for achieving balanced and controlled anesthesia, particularly in long-term procedures. Injectable induction agents play a critical role by facilitating endotracheal intubation through easy mouth opening and suppressing the pharyngolaryngeal reflex (Alexander & Clark, 1980). In this study, all anesthetic combinations provided sufficient muscle relaxation and suppression of the pharyngolaryngeal reflex, enabling successful endotracheal intubation. Sevoflurane, a widely recognized anesthetic agent for rabbits, has been reported as safe at concentrations of 3.7% to 4% (Takeda et al., 2000; Taoda et al., 2000; Weinstein et al., 2000). Consistent with the literature, sevoflurane was administered at 4% in this study and was found to be a safe and effective anesthetic agent. Heart rate showed significant decreases in all groups following the induction of anesthesia. It has been reported that propofol, midazolam, and medetomidine cause decreases in heart rate (Cruz et al., 2010; Henke et al., 2005; Kilic, 2004; Mazaheri-Khameneh et al., 2012; Rózańska, 2009). Conversely, sevoflurane and ketamine have been reported to increase heart rate due to their sympathomimetic effects (Mutoh et al., 2001; Sanford & Colby, 1980). Consistent with the literature, the observed decrease in heart rate across all groups in this study was attributed to the dominant depressive effects of propofol, midazolam, and medetomidine on the heart. When comparing groups, Group III exhibited significantly lower heart rate values than Groups I and II after anesthesia induction. The notably lower heart rate in Group III is in line with previous literature (Grint & Murison, 2008; Henke et al., 2005; Rózańska, 2009) and was associated with the dominant parasympathetic effects of medetomidine on the cardiovascular system.

Respiratory rate showed statistically significant decreases in all groups during the anesthesia period compared to baseline values, while increases were observed during the sampling times after the rabbits were disconnected from the anesthesia device. Similar to findings in the literature (Kati et al., 2003), these decreases were attributed to the depressive effects of sevoflurane on the respiratory system and the impact of catecholamines released in response to anesthesia-induced stress in rabbits. The increases in respiratory rate were associated with partial hypoxemia compensation, where stimulation of the respiratory center in the central nervous system led to rapid, shallow, and irregular breathing patterns (Hall et al., 2001). In comparisons between groups, Group III exhibited significantly lower respiratory rates at all sampling times than the other groups. This lower respiratory rate in Group III was attributed to medetomidine's pronounced respiratory depressant effects (Erol et al., 2021; Kilic, 2004; Kim et al., 2004).

General anesthesia disrupts thermoregulation in the central nervous system by inhibiting vasoconstriction and decreasing body temperature (Hall et al., 2001; Wenger, 2012). Studies on general anesthesia in rabbits have reported reductions in body temperature, attributed to impaired thermoregulation, decreased muscle activity, and reduced metabolism during anesthesia (Amarpal et al., 2014; Purohit et al., 2008). Consistent with the literature, the present study observed decreases in body temperature in all groups during the first 60 minutes of anesthesia, followed by increases after the 60th minute. However, body temperature remained below baseline values. Between-group comparisons revealed that Group I had significantly lower body temperatures than the other groups. This was attributed to propofol-induced respiratory depression, which can lead to hypotension, hypoxemia, hypercapnia, bradycardia, respiratory acidosis, and lipemia, all of which contribute to hypothermia (Brammer et al., 1993; Fujii et al., 1999; Mama et al., 1995).

Peripheral arterial hemoglobin oxygen saturation (SpO_2) increased during the anesthesia period. However, after the rabbits were disconnected from the anesthesia device, SpO_2 values decreased across all groups. This observation aligns with the literature (Hall et al., 2001), which indicates that the administration of pure oxygen via the anesthesia device leads to increased peripheral arterial hemoglobin oxygen saturation, while its cessation results in a subsequent decrease. Comparisons between groups revealed that SpO_2 levels in Group III were lower than in the other groups. This was attributed to the depressive effects of medetomidine on the respiratory system.

In order to evaluate the quality of surgical anesthesia and analgesia, no surgical procedures were

performed; instead, anesthesia depth and analgesia quality were assessed based on responses to reflex tests and pain stimuli. The results indicated that Group III demonstrated better anesthesia and analgesia quality than Groups I and II. Propofol is a short-acting, potent hypnotic agent with weak analgesic properties (Henke et al., 2005; Kilic, 2004; Orr et al., 2005). When used at high doses (1–2 mg/kg), midazolam provides excellent muscle relaxation and sedative-hypnotic effects in rabbits (Suckow et al., 2011). In this study, a 0.3 mg/kg midazolam dose was used. Studies on medetomidine and ketamine combinations in various animal species have demonstrated effective surgical anesthesia and analgesia quality (Grint & Murison, 2008; Kästner et al., 2006; Kim et al., 2004). The preference for a low dose of midazolam and the insufficient effects of propofol, consistent with findings in the literature, support the observed results.

The anesthesia sedation/induction duration was observed to be shortest in Group I, followed by Group III and then II. However, regarding quality, the groups were ranked from best to weakest, with Group III, I, and II being the weakest. Propofol, known for its high lipid solubility and rapid onset of action, is a hypnotic agent that induces anesthesia quickly (Allweiler et al., 2010; Campos et al., 2016). Consistent with the literature, Group I showed the shortest induction duration. When both the sedation/induction duration and quality were considered, the significantly lower performance of Group II was attributed to insufficient muscle relaxation at the midazolam dose (0.3 mg/kg) used in this study.

In comparisons of chewing reflex onset time (extubation time) and righting reflex duration between groups, the shortest times were observed in Group I, followed by Group II and then III. Parameters such as chewing reflex onset time, extubation time, and righting reflex duration are considered indicators of good recovery quality in rabbit anesthesia when these durations are shorter (Henke et al., 2005; Wenger, 2012). Regarding recovery quality, the best performance was observed in Group I, followed by Group II, and then III. These findings are consistent with those reported in the literature.

CONCLUSION

None of the anesthesia combinations caused severe complications or mortality. However, relative advantages were identified among the combinations. It was observed that midazolam alone, at the specified doses, was not suitable for achieving smooth and easy intubation. In this context, for both clinical and experimental procedures in rabbits, the propofol-sevoflurane combination is recommended for less painful and short-term interventions. In contrast, the medetomidine-ketamine-sevoflurane combination is more appropriate for more painful and long-term procedures.

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Conflict of Interest
The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Plan, design: YI, ME; **Material, methods and data collection:** YI, ME; **Data analysis and comments:** YI, ME; **Writing and corrections:** YI, ME.

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