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Araştırma Makalesi/ Research Article

Ratlarda Farklı Detomidin Kombinasyonlarının Klinik Olarak Karşılaştırılması

Clinical Comparison of Different Detomidine Combinations in Rats

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Özet: Bu çalışmada, ratlar üzerinde detomidin, detomidin-ketamin, detomidin-ketamin-butorfanol ve detomidin-ketamin-diazepam kombinasyonlarının klinik olarak etkileri karşılaştırıldı. Toplam 32 rat dört farklı gruba ayrıldı. Her anestezi grubunda cinsiyet dağılımı eşit olacak şekilde (4 erkek, 4 dişi) 8 adet rat yer aldı. 1. Grup D'ye (n=8) 0,1 mg/kg detomidin; 2. DK'ye (n=8) 0,1 mg/kg detomidin ve 75 mg/kg ketamin; 3.Grup DKB'ye (n=8) 0,1 mg/kg detomidin, 75 mg/kg ketamin ve 5 mg/kg butorfanol; 4. Grup DKD'ye (n=8) 0,1 mg/kg detomidin, 75 mg/kg ketamin ve 5 mg/kg diazepam intraperitoneal yolla uygulandı. Anestezi öncesi ve anestezi sonrası 5, 10, 15, 20, 25, 30, 45, 60, 90 ve 120 dakika kardiyopulmoner parametreler (kalp frekansı, solunum frekansı, vücut sıcaklığı, perifer oksijen satürasyonu) ve refleksler (pedal, palpebral, korneal, ayak parmak arası) her dört grupta incelendi. Cerrahi anestezi süresi ve toplam anestezi süresi bakımından D grubuna göre DK, DKB ve DKD grupları anlamlı düzeyde düşük (P=0,000) bulundu. Refleks parametreleri bakımından D grubuna göre pedal, palpebral ve korneal refleks kaybolma süreleri DKD grubu (P=0,035), ayak parmak arası refleksi kaybolma süresi DKD grubu (P=0,023) anlamlı düzeyde düşük bulundu. Kalp frekansı, perifer oksijen satürasyonu ve vücut sıcaklığı bakımından her dört grupta da düşüşler olduğu görüldü. Sonuç olarak, D grubu ratlarda tek başına kullanıldığında yeterli sedasyon ve anestezi oluşturmadığı tespit edildi. DKB grubu iyi bir analjezi sağladığından ağrılı özellikle ortopedik cerrahi operasyonlarda, DKD grubu ise uzun süreli anestezi sağladığından cerrahi operasyonlarda kullanımı önerilmektedir.

Anahtar Kelimeler: Anestezi, Detomidin, Kalp Frekansı, Rat, Solunum Frekansı.

Abstract: In this study, the clinical effects of detomidine, detomidine-ketamine, detomidine-ketamine-butorphanol, and detomidine-ketamine-diazepam combinations were compared in rats. A total of 32 rats were divided into four distinct groups. Each anesthesia group consisted of 8 rats with an equal sex distribution (4 males, 4 females). The experimental protocols were administered intraperitoneally as follows: Group D (n=8) received 0.1 mg/kg detomidine; Group DK (n=8) received 0.1 mg/kg detomidine and 75 mg/kg ketamine; Group DKB (n=8) received 0.1 mg/kg detomidine, 75 mg/kg ketamine, and 5 mg/kg butorphanol; and Group DKD (n=8) received 0.1 mg/kg detomidine, 75 mg/kg ketamine, and 5 mg/kg diazepam. Cardiopulmonary parameters (heart rate, respiratory rate, body temperature, peripheral oxygen saturation) and reflexes (pedal, palpebral, corneal, and interdigital) were evaluated in all four groups before anesthesia and at 5, 10, 15, 20, 25, 30, 45, 60, 90, and 120 minutes post-anesthesia. In terms of surgical and total anesthesia duration, the DK, DKB, and DKD groups were found to be significantly lower compared to Group D (P=0.000). Regarding reflex parameters, the disappearance times for pedal, palpebral, and corneal reflexes in the DKD group (P=0.035) and the interdigital reflex in the DKD group (P=0.023) were significantly shorter than those in Group D. Decreases in heart rate, peripheral oxygen saturation, and body temperature were observed across all four groups. In conclusion, it was determined that detomidine alone (Group D) did not provide adequate sedation or anesthesia in rats. The DKB combination is recommended for painful procedures, particularly orthopedic surgeries, due to its effective analgesia, while the DKD combination is suggested for surgical operations requiring prolonged anesthesia.

Keywords: Anesthesia, Detomidine, Heart Rate, Rat, Respiratory Rate.

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INTRODUCTION

The environment holds significant importance for the living space of an organism. It requires physical resources for growth, survival, and reproduction. While it is possible for some organisms to reside within a single habitat type, others necessitate the provision of specific and diverse resources. Consequently, living spaces are formed across different habitats. These organisms perceive habitat characteristics at various scales and adapt to those environments (Cox et al., 2000).

Laboratory rats continue to serve as the cornerstone of biomedical research. They are available in both albino and pigmented phenotypes. Established differences exist between wild and laboratory rats; for instance, laboratory rats exhibit smaller adrenal and preputial glands, achieve earlier sexual maturity, lack reproductive seasonality, and possess superior fertility. However, they have a shorter lifespan compared to their free-ranging wild counterparts (Sharp et al., 1998).

Rats possess a high metabolic rate; consequently, they require higher anesthetic dosages to achieve effective anesthesia compared to larger animals with lower metabolic rates (Oh and Narver, 2024).

Detomidine acts as an agonist of both central and peripheral α_2-adrenoceptors. It exerts its hypotensive and bradycardic effects through the activation of central α_2-adrenoceptors (Savola et al., 1985). Following administration, the drug is rapidly distributed into tissues, including the brain, extensively metabolized, and primarily excreted via urine. Detomidine is predominantly utilized in horses, where the peak sedative effect typically occurs between 5 and 20 minutes post-injection. The use of detomidine is contraindicated in subjects with severe chronic insufficiency, cerebrovascular disease, respiratory disease, or chronic renal failure. Furthermore, it should be administered with caution in patients with cardiac, hepatic, or renal impairment (Plumb, 2011).

Ketamine can be administered via intramuscular, intraperitoneal, and intravenous routes. It induces immobilization in many species. It causes moderate respiratory depression and increases blood pressure. With repeated doses, the recovery period may be prolonged, and hallucinations or mood alterations may be observed. In all species, the concurrent use of atropine or glycopyrrolate with these anesthetics may be required to reduce excessive bronchial and salivary secretions. In rats, ketamine is utilized at a dosage of 75 mg/kg (Flecknell, 2009).

Butorphanol is a synthetic opioid agonist-antagonist characterized by low affinity for μ-receptors (exhibiting antagonistic effects) and moderate affinity for κ-receptors (exhibiting agonistic effects). Stimulation of κ-receptors induces analgesia; however, administration at higher doses may result in dysphoria (a profound sense of restlessness). Butorphanol is metabolized in the liver into hydroxybutorphanol, an inactive metabolite excreted predominantly via bile and, to a lesser extent, through urine. While its side effects are comparable to those of most other opioids, its administration leads to increases in systemic and pulmonary pressures, as well as cardiac output. Consequently, it should be utilized with caution in patients with preexisting cardiac disease (McKeen and Quraishi, 2013). For its analgesic effect, butorphanol is administered to rats at a dosage of 1-2 mg/kg (Flecknell, 2009a).

Diazepam is one of the most common benzodiazepines administered to contemporary veterinary patients (Rankin, 2017). It induces central muscle relaxation by inhibiting polysynaptic reflexes in the spinal cord. However, surgical anesthesia can only be achieved when used in combination with other central depressant agents. The cardiovascular effects of diazepam are minimal; myocardial contractility is not significantly impaired, though a slight decrease in blood pressure may occur as a result. Heart rate remains stable or may

increase slightly. Furthermore, diazepam exerts only a minor influence on respiration, with negligible changes in respiratory rate, tidal volume, and minute ventilation. In cases of benzodiazepine overdose or excessive effect, the condition can be reversed by administering the specific benzodiazepine antagonists flumazenil or sarmazenil (Kılıç ve Erkut, 2002). For mild sedation, diazepam is utilized at a dosage of 2.5–5.0 mg/kg (Flecknell, 2009b).

MATERIALS AND METHODS

Animals

The study was conducted on a total of 32 Sprague-Dawley rats, comprising 16 males and 16 females. The rats were housed in a controlled environment under a 12-hour light/dark cycle in a well-ventilated room with a relative humidity of 40-60% and a temperature of 20-24°C. The animals were fed a commercial pellet diet (Korkutelim Feed and Food 2023, Antalya, Turkey), and water was provided ad libitum. Wood shavings were utilized as bedding material. Prior to the administration of general anesthesia, all rats underwent a standardized clinical examination.

Anaesthetic protocol

A total of 32 rats were used in the study. Each anesthesia group consisted of 8 rats with an equal sex distribution (4 males, 4 females). The experimental groups were organized as follows: Group D (n=8) received 0.1 mg/kg detomidine (Domosedan, Pfizer, 1 mg/ml); Group DK (n=8) received 0.1 mg/kg detomidine and 75 mg/kg ketamine (Ketasol, Richter Pharma, 10%); Group DKB (n=8) received 0.1 mg/kg detomidine, 75 mg/kg ketamine, and 5 mg/kg butorphanol (Butomidor, Richter Pharma, 10 mg/ml); and Group DKD (n=8) received 0.1 mg/kg detomidine, 75 mg/kg ketamine, and 5 mg/kg diazepam (Diazem, Deva Holding, 10 mg/2 ml) via the intraperitoneal (IP) route.

In Group D, values were recorded following the observation of sedation after the injection. In the dual anesthesia combination group, ketamine was administered considering the onset time of sedation following the preanesthetic injection. In the triple anesthesia combinations, the third injections were performed once the effects of ketamine were observed (i.e., upon the formation of muscle relaxation).

The anesthetized rats were placed in dorsal recumbency, and a custom-fitted oxygen mask was applied. For bedside monitoring, the red electrode was placed on the skin surface of the right forelimb, the yellow electrode on the left forelimb, and the green electrode on the umbilical region. A pulse oximeter was attached to the base of the tail to monitor the heart rate. Conductive gel was applied to the contact points to ensure optimal electrical conductivity between the skin and the electrodes.

Cardiopulmonary parameters (heart rate, respiratory rate, body temperature, and peripheral oxygen saturation) and reflexes (pedal, palpebral, corneal, and interdigital) were monitored and recorded at baseline (pre-anesthesia) and at 5, 10, 15, 20, 25, 30, 45, 60, 90, and 120 minutes post-anesthesia.

To prevent ocular dryness during the procedure, 0.9% isotonic sodium chloride solution was instilled into the eyes of the rats every 10 minutes.

Statistical evaluation and data processing

The data obtained in this study were tabulated and presented using descriptive statistics according to measurement time points and experimental groups. The normality of data distribution was assessed using the

Kolmogorov-Smirnov test. For comparative analysis, repeated measures analysis of variance (ANOVA) was employed for normally distributed data, while the Kruskal-Wallis ANOVA was used for data that did not meet the normality criteria. Through these analyses, the statistical significance of changes associated with group, time, and group-time interactions was determined. Statistical significance was set at $P < 0.05$ for all tests, and all procedures were conducted using the SPSS 22.0 software package.

RESULTS

Following intraperitoneal injection, the onset of sedative effects was observed at 4.50±0.32 minutes in Group D, 3.50±0.56 minutes in Group DK, 4.38±0.75 minutes in Group DKB, and 2.63±0.26 minutes in Group DKD. No significant difference was found between the groups in terms of anesthesia duration (P=0.055).

Heart rate findings

The effects of anesthesia protocols on heart rate findings are presented in Table 1 and Figure 1. In the D group, a decline was recorded following the injection throughout the anesthesia period. In rats receiving the injection, the heart rate decreased from an initial value of 251.75 ±14.98 bpm at the onset of anesthesia to 225.00±13.96 bpm at the 60th minute. At the 120th minute, the heart rate was measured at 240.37±3.94 bpm, which was close to the baseline value (P=0.331).

In the DK group, the baseline value was 208.75±14.08 bpm; after the heart rate rose to 241.25±13.34 bpm at the 10th minute of anesthesia, a subsequent decrease was observed throughout the anesthetic period (P=0.194).

Similarly, a slight increase in heart rate was observed in the DKB group at the 10th and 15th minutes of anesthesia, whereas statistically significant decreases (P=0.002) were recorded at the 30th, 45th, 90th and 120th minutes.

In the DKD group, a statistically significant (P=0.011) decrease was observed at the 45th, 60th and 90th minutes from an initial heart rate of 232.87±21.92 bpm. At the 120th minute, the heart rate reached 213.87 ±14.00 bpm, approaching the baseline value.

In the intergroup evaluation, the mean value of the DKB group was found to be significantly lower than that of the detomidine group at the 30th minute of the study (P=0.007). At the 90th minute, the DK, DKB and DKD groups exhibited significantly lower values compared to the detomidine group (P=0.006). Furthermore, at the 120th minute, the values for the DK and DKB groups remained significantly lower than those of the detomidine group (P=0.037).

Table 1. Effect of anesthesia groups on heart rate (bpm) levels

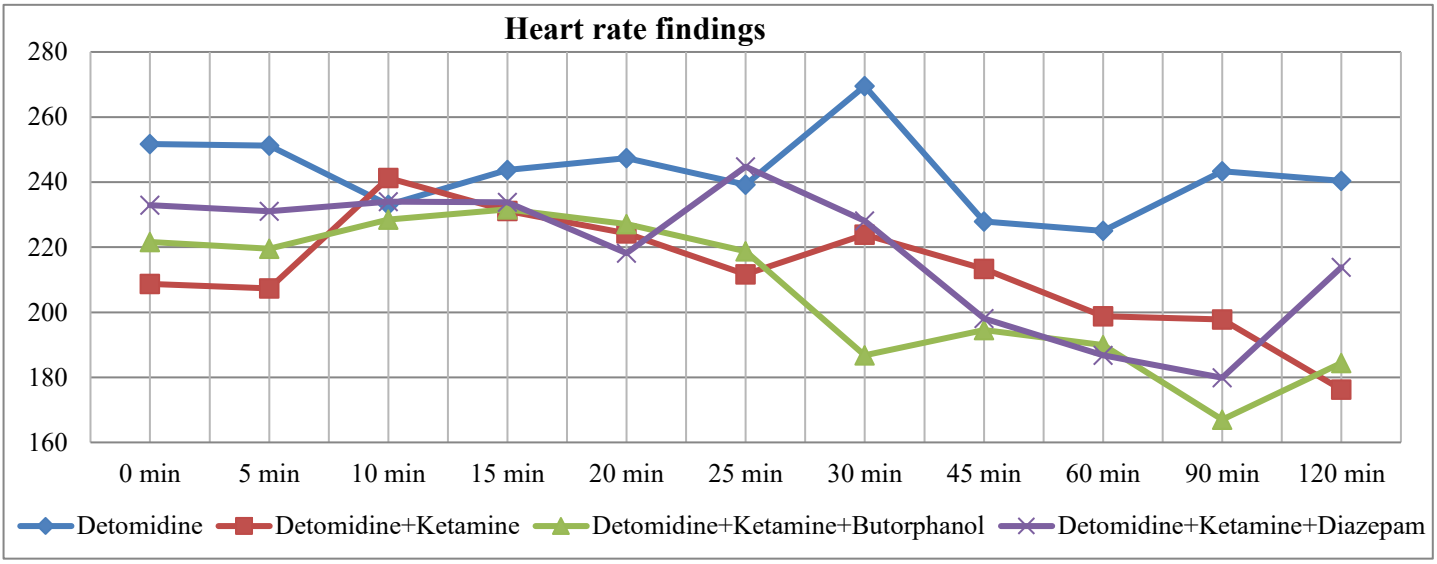
	Heart rate findings (X±Sx)											
	0 min	**5 min**	**10 min**	**15 min**	**20 min**	**25 min**	**30 min**	**45 min**	**60 min**	**90 min**	**120 min**	**P**
Detomidine	251.75±14.98	251.25±15.20	233.00±18.28	243.75±18.11	247.37±12.00	239.25±7.89	269.50±9.54	227.87±17.55	225.00±13.96	243.37±3.94	240.37±3.94	0.331

Detomidine +Ketamine	208.75± 14.08	207.37± 14.03	241.25± 13.34	231.12± 16.97	224.25± 11.88	211.62± 20.03	223.87±1 6.76	213.37±1 8.04	198.75±4 .99	197.75±1 7.81*	176.25±1 8.60*	0.1 94
Detomidine +Ketamine +Butorphanol	221.62± 13.01	219.50± 12.74	228.50± 12.98	231.62± 7.18	227.12± 9.39	218.75± 11.26	186.75±1 3.16*†	194.50±9 .95†	189.87±1 3.24	167.00±1 6.95*†	184.37±2 1.06*†	**0.0 02**
Detomidine +Ketamine +Diazepam	232.87± 21.92	231.00± 21.82	234.00± 18.00	233.75± 13.97	218.12± 21.79	244.75± 18.74	228.12±1 9.58	198.12±1 8.24†	186.75±1 7.36†	179.87±1 5.36*†	213.87±1 4.00	**0.0 11**
P	0.314	0.292	0.953	0.921	0.528	0.376	**0.007**	0.464	0.184	**0.006**	**0.037**	

*: Mean values in the same column are significantly different from the detomidine group

†: Mean values in the same row are significantly different from the baseline group

Figure 1. The effect of anesthesia groups on heart rate (bpm) levels



Respiratory rate findings

The findings regarding the effects of the groups on respiratory rate are presented in Table 2 and Figure 2. In Group D rats, fluctuations were observed following the injection. Values initially recorded as 65.75±17.41 breaths/min increased to 77.87±19.20 breaths/min at the 15th minute and subsequently declined to 64.50±10.64 breaths/min by the 120th minute (P=0.943).

In the DK group, the baseline value started at 111.87±12.73 breaths/min. The respiratory rate rose to 123.25±15.58 breaths/min at the 10th minute of anesthesia and decreased to 89.87±9.72 breaths/min at the 25th minute. However, the rate increased again to 124.25±9.89 breaths/min at the 45th minute, eventually being recorded as 93.25±14.59 breaths/min at the 120th minute (P=0.112).

In the DKB group rats, the respiratory rate began at 104.00±18.11$ breaths/min and a deceleration to 86.62±14.75 breaths/min was observed at the 30th minute. The respiratory increase reached 103.87±16.06 breaths/min at the 45th minute and 105.12±11.07 breaths/min at the 60th minute, ending at 100.12±14.45 breaths/min at the 120th minute (P=0.365).

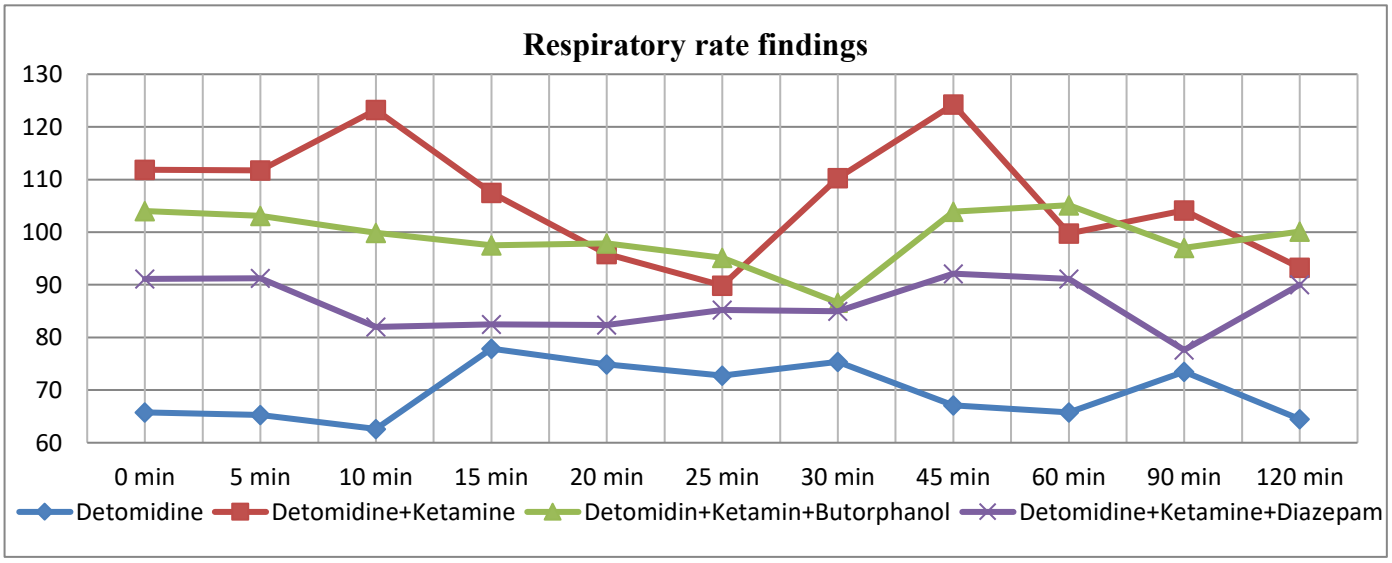
In the DKD group rats, respiratory levels followed a steady course post-anesthesia. The respiratory rate started at 91.12±6.49 breaths/min and was measured as 90.00±9.66 breaths/min at the 120th minute (P=0.970).

When evaluating the intergroup differences in the study, no statistically significant changes were observed regarding the effect on respiratory rate levels.

Table 2. Effects of anesthesia groups on respiratory rate (breaths/min) levels

	Respiratory rate findings (X±SX)											
	0 min	**5 min**	**10 min**	**15 min**	**20 min**	**25 min**	**30 min**	**45 min**	**60 min**	**90 min**	**120 min**	**P**
Detomidine	65.75±17.41	65.25±17.74	62.62±18.62	77.87±19.20	74.87±15.13	72.75±17.72	75.37±17.04	67.12±19.42	65.75±15.46	73.50±12.20	64.50±10.64	0.943
Detomidine +Ketamine	111.87±12.73	111.75±12.79	123.25±15.58	107.50±13.62	95.87±10.75	89.87±9.72	110.25±11.22	124.25±9.89	99.75±12.02	104.12±14.55	93.25±14.59	0.112
Detomidine +Ketamine +Butorphanol	104.00±18.11	103.12±18.11	99.87±16.68	97.50±13.32	97.87±14.96	95.12±16.28	86.62±14.75	103.87±16.06	105.12±11.07	97.00±10.64	100.12±14.45	0.365
Detomidine +Ketamine +Diazepam	91.12±6.49	91.25±7.27	82.00±9.21	82.50±8.82	82.37±11.57	85.25±14.35	85.00±12.87	92.12±9.62	91.12±10.46	77.62±12.78	90.00±9.66	0.97
P	0.144	0.152	0.06	0.444	0.566	0.743	0.366	0.061	0.141	0.27	0.226	

Figure 2. Effect of anesthesia groups on respiratory rate (breaths/min) levels



Body temperature findings

The effects of anesthesia protocols on body temperature findings are presented in Table 3 and Figure 3. In rats administered with D, the body temperature was observed to be 37.88±0.33°C at the time of injection. Although it rose to 38.03±0.14°C at the 15th minute, a subsequent decline in body temperature occurred in

the following minutes. Statistically significant decreases (P=0.000) compared to the baseline values were recorded at the 60th, 90th and 120th minutes. At the 120th minute, the body temperature was measured as 36.62±0.30°C.

In the DK group, body temperature started at 37.65±0.29°C, and a continuous decline was recorded throughout the anesthesia period. Body temperature decreased to 36.21±0.44°C at the 45th minute and to 36.80±0.77°C at the 120th minute of the study. Statistically significant decreases (P=0.001) relative to the baseline were recorded at the 15th, 20th, 25th, 30th, 45th, 60th, 90th and 120th minutes.

In the DKB group, the body temperature started at 37.72±0.24°C. A decline was recorded throughout the duration of anesthesia, with the body temperature reaching 35.40±0.59°C at the 120th minute. Statistically significant decreases (P=0.000) compared to the baseline values were observed from the 25th minute onwards.

In the DKD group, the body temperature was 37.85±0.24°C at the time of injection. It was observed to drop to 35.40±0.41°C by the 120th minute. The decreases detected at the 25th, 30th, 45th, 60th, 90th and 120th minutes were found to be statistically significant (P=0.000) compared to the baseline values.

Table 3. Effects of anesthesia groups on body temperature (°C) levels over time

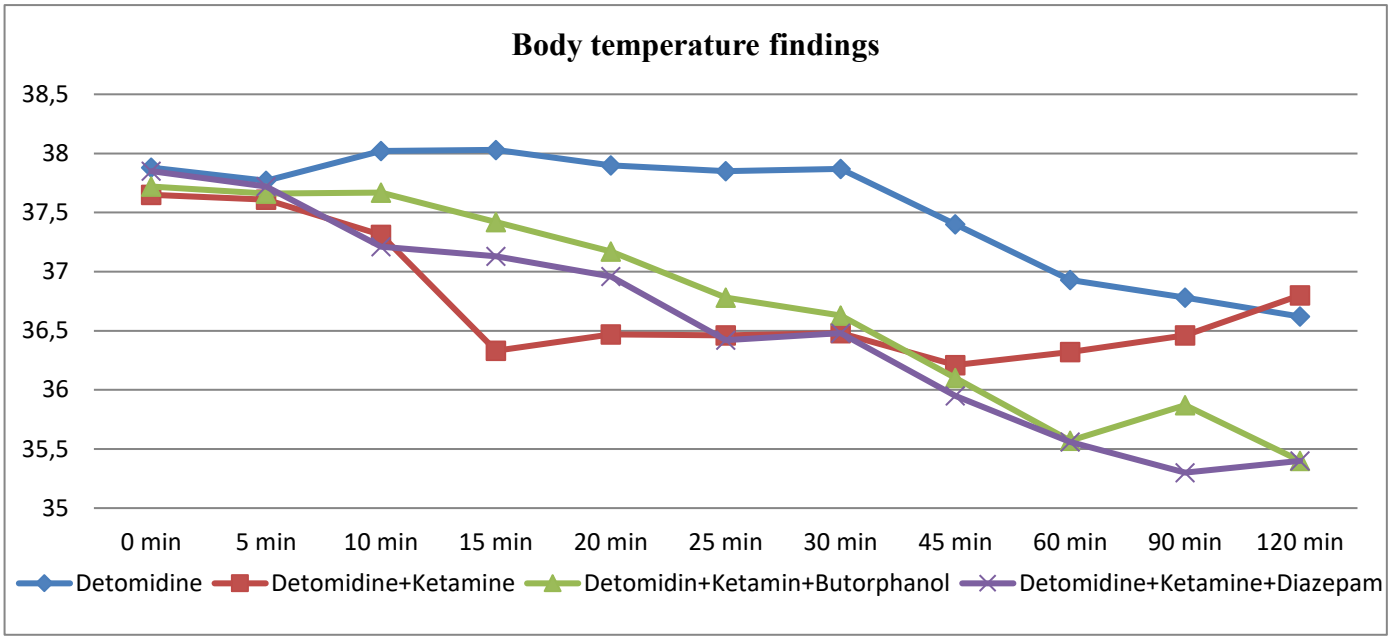
	Body temperature findings (X±Sx)											
	0 min	**5 min**	**10 min**	**15 min**	**20 min**	**25 min**	**30 min**	**45 min**	**60 min**	**90 min**	**120 min**	**P**
Detomidine	37.88±0.33	37.77±0.34	38.02±0.18	38.03±0.14	37.90±0.16	37.85±0.16	37.87±0.27	37.40±0.27	36.93±0.24†	36.78±0.12†	36.62±0.30†	**0**
Detomidine +Ketamine	37.65±0.29	37.61±0.30	37.31±0.32	36.33±0.35*†	36.47±0.30*†	36.46±0.36*†	36.48±0.29*†	36.21±0.44*†	36.32±0.47†	36.46±0.72†	36.8±0.77†	**0.001**
Detomidine +Ketamine +Butorphanol	37.72±0.24	37.66±0.28	37.67±0.25	37.42±0.25	37.17±0.25	36.78±0.34*†	36.63±0.26*†	36.10±0.22*†	35.57±0.41†	35.87±0.49†	35.40±0.59†	**0**
Detomidine +Ketamine +Diazepam	37.85±0.24	37.72±0.27	37.21±0.39	37.13±0.29*	36.96±0.36*	36.42±0.44*†	36.48±0.36*†	35.95±0.47*†	35.56±0.37†	35.30±0.43†	35.40±0.41†	**0**
P	0.926	0.983	0.234	**0.002**	**0.013**	**0.022**	**0.007**	**0.038**	0.051	0.178	0.344	

*: Mean values in the same column are significantly different from the detomidine group

†: Mean values in the same row are significantly different from the baseline group

In the intergroup evaluation, values in the DK and DKD groups were significantly lower than those in the detomidine group at the 15th (P=0.002) and 20th minutes (P=0.013). Furthermore, at the 25th (P=0.022), 30th (P=0.007) and 45th minutes (P=0.038), the DK, DKB, and DKD groups were determined to be significantly lower compared to the detomidine group.

Figure 3. Effect of anesthesia groups on body temperature (°C) levels over time



SpO_2 findings

The effects of anesthesia protocols on SpO_2findings are presented in Table 4 and Figure 4. In Group D, a decrease in SpO_2 levels was recorded following the injection throughout the anesthesia period. The SpO_2 level, which was %91.00±1.61 at baseline, declined to %85.37±3.54 at the 90th minute of anesthesia. Subsequently, it increased to %86.50±1.25 at the 120th minute (P=0.658).

In the rats of the DK group, the SpO_2 level remained at %86.00±3.85 during the first 10 minutes post-injection and rose to %95.25±0.99 at the 20th minute of anesthesia. Thereafter, it showed a continuous decline, receding to %89.12±3.32 by the 120th minute, a value close to the baseline level (P=0.649).

In the DKB group, SpO_2 levels started at %89.75±2.56\%$ and increased to %92.00±2.18 at the 10th minute. The SpO_2 level, which dropped to %84.00±3.81 at the 20th minute, rose again to %92.87± 2.04 at the 60th minute. In the later minutes of anesthesia, a decrease was recorded, falling to %81.75±4.96 at the 120th minute (P=0.612).

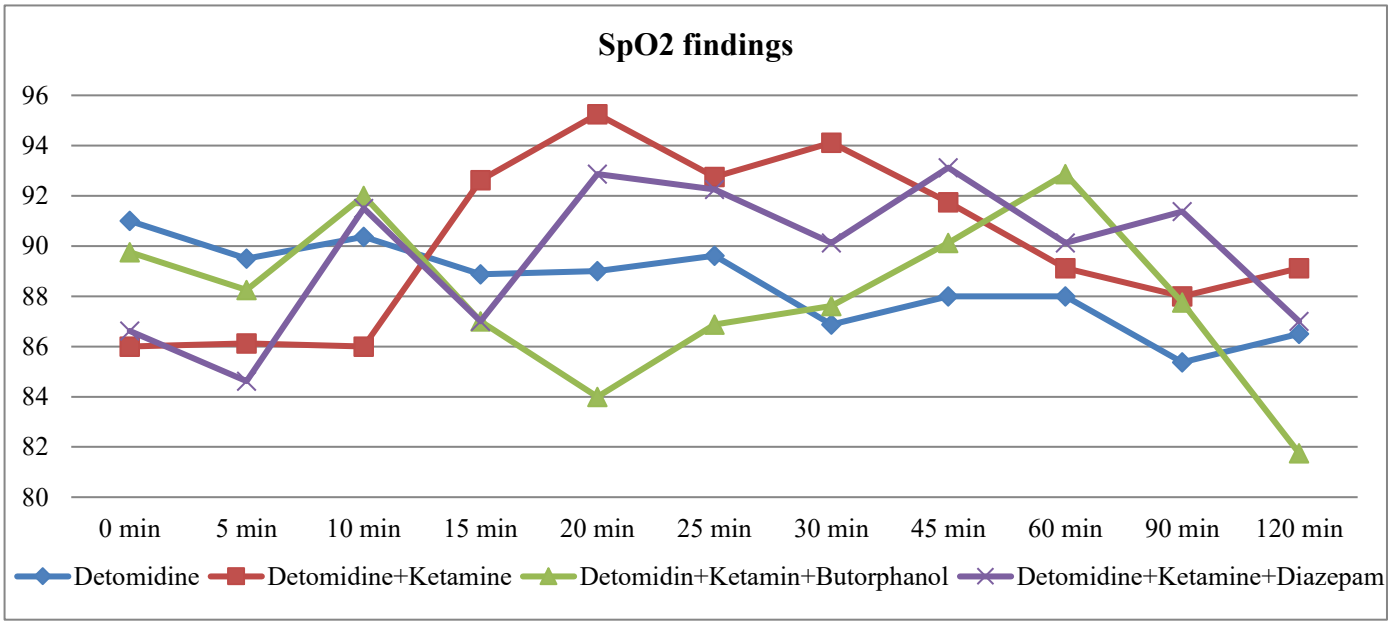
In the DKD group, the SpO_2 level started at %86.62±2.23 and reached %91.50±3.25 at the 10th minute. The SpO_2 level, which decreased to %87.00±3.41 at the 15th minute, increased to %93.12±2.06 at the 45th minute and receded to %87.00±3.66 by the 120th minute, near the initial level.

When evaluated between groups, no statistically significant difference was observed regarding the effects on SpO_2 levels throughout the study.

Table 4. Effects of anesthesia groups on SpO_2 (%) levels

	SpO_2 findings (X±Sx)											
	0 min	**5 min**	**10 min**	**15 min**	**20 min**	**25 min**	**30 min**	**45 min**	**60 min**	**90 min**	**120 min**	**P**
Detomidine	91.00±1.61	89.50±2.20	90.37±2.08	88.87±1.84	89.00±4.11	89.62±4.28	86.87±3.25	88.00±2.18	88.00±3.63	85.37±3.54	86.50±1.25	0.658
Detomidine +Ketamine	86.00±3.76	86.12±3.99	86.00±3.85	92.62±2.34	95.25±0.99	92.75±1.65	94.12±1.58	91.75±3.42	89.12±3.98	88.00±4.76	89.12±3.32	0.649
Detomidine +Ketamine +Butorphanol	89.75±2.56	88.25±2.83	92.00±2.18	87.00±2.89	84.00±3.81	86.87±4.01	87.62±4.07	90.12±3.22	92.87±2.04	87.75±2.25	81.75±4.96	0.612
Detomidine +Ketamine +Diazepam	86.62±2.23	84.62±2.28	91.50±3.25	87.00±3.41	92.87±3.27	92.25±2.49	90.12±3.93	93.12±2.06	90.12±3.03	91.37±2.28	87.00±3.66	0.267
P	0.493	0.65	0.472	0.42	0.106	0.575	0.432	0.605	0.747	0.662	0.525	

Figure 4. Effect of anesthesia groups on SpO_2 (%) levels



Reflex findings

The effects of anesthetics on reflex parameters are presented in Table 5. Following injection, the sedative effect was observed at a mean of 270.00±19.64 seconds in the D group, 188.75±23.86 seconds in the DK group, 255.00±47.77 seconds in the DKB group, and 157.50±15.78 seconds in the DKD group.

The duration of surgical anesthesia was determined as a mean of 3547.50±230.55 seconds (approximately 59 minutes) in the D group, 21778.75±789.13 seconds (approximately 363 minutes) in the DK group, 24187.50±89.59 seconds (approximately 403 minutes) in the DKB group, and 33157.50± 428.02 seconds (approximately 553 minutes) in the DKD group.

The disappearance times of the pedal reflex, palpebral reflex, and corneal reflex were significantly lower in the DKD group compared to the D group (P=0.035). Furthermore, the disappearance time of the interdigital reflex (toe pinch reflex) was found to be statistically significantly lower in the DKD group than in the D group (P=0.023).

The duration of surgical anesthesia and total anesthesia time were significantly lower (P=0.000) in the DK, DKB, and DKD groups compared to the D group.

Table 5. Evaluation of various reflexes, surgical anesthesia duration, and total anesthesia time (s) across anesthesia groups

Parameters (s) (X±Sx)	**Groups**				**P**
	Detomidine	**Detomidine+Ketamine**	**Detomidine+Ketamine+Butorphanol**	**Detomidine+Ketamine+Diazepam**	
Time to Loss of Pedal Reflex	270.00±19.64	188.75±23.86	255.00±47.77	157.50±15.78*	**0.035**
Time to Loss of Palpebral Reflex	270.00±19.64	188.75±23.86	255.00±47.77	157.50±15.78*	**0.035**
Time to Loss of Corneal Reflex	270.00±19.64	188.75±23.86	255.00±47.77	157.50±15.78*	**0.035**
Time to Loss of Interdigital Reflex	277.50±19.43	188.75±23.86	292.50±59.39	157.50±15.78*	**0.023**
Duration of Surgical Anesthesia	3547.50±230.55	21778.75±789.13*	24187.50±89.59*	33157.50±428.02*	**0**
Total Duration of Anesthesia	3915.00±276.76	22371.25±691.65*	24465.00±98.03*	33457.50±397.66*	**0**

*: Mean values within the same row differ significantly from the detomidine group (P<0.05).

DISCUSSION

The study aimed to investigate the clinical efficacy of detomidine and its combinations in rats. Detomidine (an α_2-adrenoreceptor agonist), diazepam (a benzodiazepine), and butorphanol (an opioid) were administered as preanesthetic agents, while ketamine was utilized for anesthetic induction.

Heart rate

Regarding the effects of anesthetic combinations on heart rate over time, a decrease was observed in the detomidine group throughout the anesthesia period following injection; baseline values of approximately 251 bpm decreased to around 240 bpm by the 120th minute. In the DK group, heart rate increased at the 10th minute post-injection but declined as anesthesia progressed. Statistically significant decreases were recorded in the DKB group at the 30th, 45th, 90th and 120th minutes (P=0.002), and in the DKD group at the 45th, 60th and 90th minutes (P=0.011).

A previous study investigating the effects of detomidine on norepinephrine release and turnover in the rat brain reported that detomidine induces post-anesthetic bradycardia (Virtanen, 1986). In alignment with these findings, a decrease in heart rate was observed throughout anesthesia in our study.

In the DK group, tachycardia developed at the 10th minute post-injection due to central nervous system stimulation by ketamine; however, subsequent decreases in heart rate were observed. This initial increase is thought to be a result of the positive inotropic effect of ketamine. The baseline heart rate, measured at approximately 208 bpm, was observed to decline to about 176 bpm by the 120th minute of anesthesia.

The DKB combination resulted in a more pronounced decrease in heart rate compared to other groups. It is suggested that butorphanol, an opioid, caused bradycardia through the stimulation of the central vagal nucleus.

In the DKD group, the combination of ketamine and diazepam is thought to have caused bradycardia during anesthesia exceeding the first 30 minutes, likely due to muscle relaxation resulting from the inhibition of polysynaptic reflexes in the spinal cord. The statistical significance observed at the 45th minute supports this conclusion.

Respiratory rate

Regarding the effects of anesthetic combinations on respiratory rate over time, no significant changes were observed. This lack of significance is attributed to the administration of 100% oxygen supplementation whenever SpO_2 levels dropped below 80% during the study.

It has been reported in the literature that the average respiratory rate of a rat is approximately 85 breaths/min (Fox, 2015). In the present study, the group administered detomidine alone started with an initial mean value of approximately 65 breaths/min, returning to a near-baseline mean of 64 breaths/min at the 120th minute. It was observed that detomidine induced respiratory depression in this group when administered as a sole agent.

A study comparing the effects of xylazine, detomidine, and medetomidine on heart rate, respiratory rate, and blood glucose levels in sheep reported that respiratory rates increased within the first 15 minutes with detomidine, followed by a decrease at the 40th minute (Malhi et al., 2015). Despite the difference in animal species, the rats in our study's detomidine-only group similarly exhibited an increase in respiratory frequency within the first 15 minutes, followed by a decline at the 45th minute. Both studies are consistent regarding the effects of detomidine anesthesia on respiration.

In the DK group, the respiratory rate started at approximately 111 breaths/min, showed variability, and declined to approximately 93 breaths/min at the 120th minute. In the DKB group, the initial rate was recorded at approximately 104 breaths/min, decreasing to 100 breaths/min at the 120th minute. For the DKD group, the respiratory frequency began at a mean of 91 breaths/min and reached a near-baseline mean of 90 breaths/min by the 120th minute.

A study evaluating detomidine anesthetic combinations in rabbits identified that, among the groups (detomidine alone, detomidine-ketamine, high-dose detomidine-ketamine, and detomidine-ketamine-diazepam), detomidine monotherapy caused the least respiratory depression (Hurley et al., 2013). Conversely, in our study, the detomidine-only group exhibited the highest degree of respiratory depression, while the DKD group showed the least. This discrepancy is thought to arise from the physiological differences between the animal families used in the respective studies.

Body temperature

Regarding the effects of anesthetic combinations on body temperature over time, a statistically significant decrease was recorded in Group D at the 60th, 90th and 120th minutes compared to baseline values (P=0.000).

In Group DK, significant decreases (P=0.001) were observed at the 15th, 20th, 25th, 30th, 45th, 60th, 90th and 120th minutes. Similarly, in Group DKB and Group DKD, significant reductions (P=0.000) were recorded at the 25th, 30th, 45th, 60th, 90th and 120th minutes.

When evaluating intergroup differences in body temperature, values were significantly lower compared to Group D as follows: in Group DK and Group DKD at the 15th minute (P=0.002); in Group DK and Group DKD at the 20th minute (P=0.013); in Groups DK, DKB, and DKD at the 25th minute (P=0.022); in Groups DK, DKB, and DKD at the 30th minute (P=0.007); and in Groups DK, DKB, and DKD at the 45th minute (P=0.038).

Normal body temperature in rats, measured via rectal or tympanic membrane thermometry, ranges between 35.9–37.5°C (2). Deep anesthesia is required for prolonged surgical interventions; however, anesthetized subjects cannot maintain physiological body temperature (Redfords et al., 2013). Consequently, a decline in body temperature is observed. In this study, to prevent hypothermia-related mortality, rats were heated using warm water bags when their body temperature approached 36°C during anesthesia.

SpO_2 levels

Regarding the effects of anesthetic combinations on SpO_2 levels, no statistically significant changes were observed. Throughout the study, the SpO_2 levels of the rats were monitored, and 100% oxygen supplementation was initiated as soon as the levels began to decline toward approximately 85%.

In a previous study, the physiological effects of isoflurane, sevoflurane, and hypothermia used during anesthesia in neonatal rats (*Rattus norvegicus*) were investigated. It was concluded that both isoflurane and sevoflurane anesthesia induced hypothermia in 4-day-old rat pups while maintaining physiological parameters (heart rate, respiratory rate, and SpO_2) within normal ranges (Huss et al., 2016). Compared to our findings, the younger age of the rats and the utilization of different anesthetic combinations in that study are thought to be the factors leading to these discrepancies.

Another study compared the intraperitoneal tolerance of ketamine-xylazine and ketamine-dexmedetomidine anesthesia using Wistar Han rats. It was reported that the administration of ketamine-dexmedetomidine resulted in a 20% decrease in heart rate, a 33% decrease in respiratory rate, and a 20% reduction in peripheral oxygen saturation compared to baseline levels (Wellington et al., 2013). These findings do not support our results. In our study, the SpO_2 levels in the DK group remained at approximately 86% during the first 10 minutes, rose to 95.25% at the 20th minute, and concluded at 89.12% at the 120th minute, which was higher than the baseline value. This difference is attributed to the administration of 100% oxygen at the onset of anesthesia.

Reflexes

Reflexes were monitored during the injection process and throughout the duration of anesthesia in all groups, and each data point was recorded. To assess the palpebral reflex, the medial canthus of the eye was touched with the tip of a clamp to check for a response. For the corneal reflex, the surface of the cornea was gently touched with a finger to observe any reaction. To prevent ocular dryness during the study, 0.9% isotonic sodium chloride solution was instilled into the eyes every 10 minutes. The interdigital reflex was evaluated by pinching the interdigital tissue of the rats with a clamp. Reactions to stimuli were recorded as positive responses.

Regarding the onset of sedation and the disappearance of palpebral, corneal, and pedal withdrawal reflexes, the earliest onset was observed in the DKD group, occurring within a mean of 157.50±15.78 seconds (approximately 2.5 minutes). In contrast, the latest onset was recorded in the D group, with a mean of 270.00±19.64 seconds (approximately 4.5 minutes). The duration of sedation onset was 188.75±23.86 seconds (approx. 3 minutes) in the DK group and 255.00±47.77 seconds (approx. 4 minutes) in the DKB group.

When groups were compared in terms of the duration of surgical anesthesia, the longest duration was identified in the DKD group (33157.50±428.02 seconds; approx. 553 minutes), while the shortest duration was found in the D group (3547.50±230.55 seconds; approx. 59 minutes).

Detomidine, similar to medetomidine, belongs to the class of α_2-adrenoceptor agonists. Medetomidine exhibits significant sedative and analgesic effects in laboratory animals and is a potent, selective anesthetic. In a previous study (Jang et al., 2009), the anesthetic effects of combined medetomidine and ketamine doses were compared in male rats weighing an average of 341±26 grams. Rats divided into three groups received medetomidine (0.2, 0.4, and 0.8 mg/kg) and ketamine (60 mg/kg). It was reported that the pedal withdrawal reflex disappeared within 600 seconds (10 minutes) in rats receiving 0.2 and 0.4 mg/kg, and that the duration of surgical anesthesia significantly increased with higher medetomidine doses. In our study, the pedal withdrawal reflex in the DK group disappeared within 188.75±23.86 seconds (approx. 3 minutes). Comparing the two studies, detomidine anesthesia demonstrated a more rapid onset of action than medetomidine anesthesia.

A review of the current literature revealed no other studies comparing the clinical parameters of detomidine and its combinations in rats. Therefore, it is anticipated that this study will be promising in its field and that the measurements and results obtained will provide a significant contribution to the literature.

CONCLUSION AND RECOMMENDATIONS

The rats utilized in this study were monitored for a one-week acclimation period. Following the confirmation of their health status via physical examinations, the clinical efficacy of experimentally administered D, DK, DKB, and DKD anesthetic combinations was comparatively investigated. Since detomidine is primarily utilized in horses and cattle, research involving its use in rats remains considerably limited. This study aimed to evaluate the effects of detomidine, both alone and in various anesthetic combinations, on clinical parameters in rats.

In conclusion, the comparison of anesthetic groups revealed that while mild sedation was achieved in the D group, deep sedation was observed in the DK, DKB, and DKD groups. Compared to the D group, the DK group exhibited a shorter induction time and a prolonged duration of surgical anesthesia. The addition of butorphanol to the DK combination (DKB) resulted in a shorter induction time relative to the D group, yet it was longer than that of the DK group. The DKB group provided effective analgesia, and the duration of surgical anesthesia was longer than both the D and DK groups. The addition of diazepam to the DK combination (DKD) yielded the shortest induction time and the longest duration of surgical anesthesia among all four groups.

All four anesthetic combinations administered in the study caused a decrease in heart rate; this decline was statistically significant in the DKB and DKD groups.

Respiratory depression and a decrease in SpO_2 levels were observed in all combinations, with the most pronounced effect occurring in the DKB group. To prevent further decline, 100% oxygen supplementation was initiated when SpO_2 levels reached approximately 85%.

Decreases in body temperature were recorded across all four anesthetic combinations. To prevent anesthesia-induced hypothermia throughout the procedure, the rats were closely monitored, and external heat sources were applied when body temperatures dropped below 36°C.

As detomidine (D) anesthesia alone does not provide adequate sedation or anesthesia in rats, its solitary use is not recommended. The DKB combination is suggested for painful procedures due to its superior analgesic properties, while the DKD combination is recommended for surgical interventions requiring prolonged anesthesia.

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Research and Publication Ethics

This study was carried out with the approval of Aydın Adnan Menderes University Animal Experiments Local Ethics Committee (ADU-HADYEK) dated 13.04.2023 and numbered 64583101/2023/53.

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