RESEARCH ARTICLE

F.U. Vet. J. Health Sci.
2025; 39 (3): 140 - 146
http://www.fusabil.org

Comparative Investigation of the Intraoperative Analgesic Effects of Ketoprofen, Meloxicam and Buprenorphine Used Before Orchiectomy in Rabbits *

Kerem UZUN [1, a]
Nuh KILIÇ [2, b]

[1] Ministry of Agriculture and Forestry,
Çaldıran Directorate of Agriculture and Forestry,
Van, TÜRKİYE

[2] Aydın Adnan Menderes University,
Faculty of Veterinary Medicine,
Department of Veterinary Surgery,
Aydın, TÜRKİYE

[a] ORCİD: 0000-0002-4546-4832
[b] ORCİD: 0000-0001-8452-161X

In this study, 24 male New Zealand White rabbits aged 8 months-3 years, weighing 2.5-5.5 kg, were used to examine the effectiveness of different analgesics before orchiectomy surgery. The rabbits were divided into four groups: while the control group was not given an analgesic substance, the other groups were administered meloxicam, ketoprofen and buprenorphine analgesics intramuscularly, respectively. Ten minutes after analgesic administration, all rabbits were anesthetized with medetomidine-ketamine combination. In the study, parameters such as heart rate, respiratory frequency, body temperature, SpO_2 and pain scoring was performed. Additionally, serum cortisol levels were evaluated with blood samples taken preoperatively, after anesthesia, at the end of orchiectomy, and at the 2nd, 4th and 6th hours postoperatively. The results showed that analgesic administration had significant effects on cortisol levels. Respiratory frequency did not show any significant change between the groups at each time point, however, in rabbits administered meloxicam, the preoperative measurements were significantly lower (p=0.008) compared to the intraoperative period. In rabbits administered buprenorphine, intraoperative and postoperative measurements were found to differ significantly from the preoperative measurements at (p=0.020) and (p=0.015) levels, respectively. An average decrease of 0.5°C in body temperature was observed in the meloxicam and buprenorphine groups, and anesthesia-related changes in heart and respiratory frequencies were observed. According to the level of serum cortisol, which is an acute biomarker of pain and pain response, it was concluded that the analgesic agent with the strongest analgesic effect was buprenorphine and the analgesic agent with the weakest analgesic effect was ketoprofen in the doses and administration routes specified in the study during orchiectomy operations in rabbits.

Key Words: *Pain, analgesia, intraoperative, orchiectomy, rabbit*

Tavşanlarda Orşiektomi Öncesi Kullanılan Ketoprofen, Meloksikam ve Buprenorfinin İntraoperatif Analjezik Etkilerinin Karşılaştırmalı Olarak Araştırılması

Bu çalışmada, orşiektomi operasyonu öncesi farklı analjeziklerin etkinliğini incelemek amacıyla yaşları 8 ay-3 yıl ve ağırlıkları 2.5-5.5 kg arasında değişen 24 adet erkek Yeni Zelanda Beyaz tavşanı kullanıldı. Tavşanlar dört gruba ayrıldı: kontrol grubuna analjezik bir madde verilmezken, diğer gruplara sırasıyla meloksikam, ketoprofen ve buprenorfin analjezik maddeleri intramusküler olarak uygulandı. Analjezik uygulamasından 10 dakika sonra tüm tavşanlar medetomidin-ketamin kombinasyonu ile anesteziye alındı. Çalışmada, kalp frekansı, solunum frekansı, vücut sıcaklığı, SpO2 ve ağrı skorlaması gibi parametreler değerlendirildi. Ayrıca, serum kortizol düzeyleri orşiektomi öncesi, anestezi sonrası, orşiektomi sonrası ve orşiektomi sonrası 2., 4. ve 6. saatlerde alınan kan örnekleri ile değerlendirildi. Sonuçlar analjezik uygulamasının kortizol düzeyleri üzerinde anlamlı etkileri olduğunu gösterdi. Solunum frekansı her zaman noktasında gruplar arasında anlamlı bir değişim göstermezken, meloksikam uygulanan tavşanlarda preoperatif ölçümler intraoperatif döneme kıyasla anlamlı derecede düşüktü (p=0.008). Buprenorfin uygulanan tavşanlarda intraoperatif ve postoperatif ölçümlerin sırasıyla (p=0.020) ve (p=0.015) düzeylerde preoperatif ölçümlerden anlamlı derecede farklı olduğu bulundu. Meloksikam ve buprenorfin gruplarında vücut sıcaklığında ortalama 0.5°C'lik bir düşüş gözlendi ve kalp ve solunum frekanslarında anesteziyle ilişkili değişiklikler gözlendi. Tavşanlarda orşiektomi operasyonları sırasında, akut ağrı ve ağrı yanıtı biyobelirteci olan serum kortizol düzeyine göre, çalışmada belirtilen doz ve uygulama yollarında, en güçlü analjezik etkiye sahip analjezik ajanın buprenorfin, en zayıf analjezik etkiye sahip analjezik ajanın ise ketoprofen olduğu sonucuna varıldı.

Anahtar Kelimeler: *Ağrı, analjezi, ameliyat sırasında, orşiektomi, tavşan*

Received : 17.07.2025
Accepted : 26.08.2025

Correspondence

Kerem UZUN
Ministry of Agriculture and Forestry,
Çaldıran Directorate of Agriculture and Forestry
Van – TÜRKİYE

keremuzun726@gmail.com

Introduction

Studies on laboratory animals, as in the past, are still important for humanity in many areas, including vaccine studies, discovery of new drugs, and cancer studies. The pain that occurs during these experimental studies is a major source of stress and if the necessary precautions are not taken, it negatively affects the results of the study and is also a negative situation in terms of animal welfare. Despite the large number of rabbits, the number of rabbits subjected to surgery, anesthesia, and analgesia protocols is still

* This research article is a doctoral thesis and was supported by Aydın Adnan Menderes University Scientific Research Projects Unit with project number VTF-23017.

limited compared to cats and dogs (1, 2). Three studies were conducted to classify conditions that may cause pain in rabbits. In the first study in pet rabbits, common conditions such as gastrointestinal diseases, fight injuries, neutering and painful urinary tract diseases were reported. The second study focused on the severity of pain and the operations performed on pet rabbits. Orthopedic procedures have been identified as the most painful procedure, following ovariohysterectomy, castration, and surgical treatment of abscess. In the third study in laboratory rabbits, orchiectomy and cesarean section incisions caused mild to moderate pain, while major laparotomy and organ incision were considered to cause moderate to severe pain (2-4). In this study in order to provide preemptive analgesia, different analgesic substances that have not been used before in rabbits will be used preoperatively and their intraoperative analgesic effects will be comparatively investigated and thus animal welfare will be ensured by making the animals feel less pain in future experimental studies on rabbits. In addition, it is aimed to fill the gap in the literature on this subject by contributing to increasing the accuracy and reliability of the findings of the studies.

Materials and Methods

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 14.06.2022 and numbered 64583101/2022/53.

Animals and Experimental Groups: The animal material in the study consisted of 24 male New Zealand White Rabbits (Oryctolagus cuniculus), aged 8 months-3 years, weighing 2.5-5.5 kg. Rabbits were obtained from a certified rabbit breeding farm in Manisa. Before being brought from the rabbit farm, 24 rabbits were divided into four groups (n=6) by simple randomization method and placed in numbered individual cages. Wood shavings and wheat straw were used as bedding materials. The environment in which the animals were housed was at a temperature of 18-22°C. Ad-libitum feeding consisting of standard rabbit chow and dry alfalfa was provided to the rabbits, and they were housed for 7 days to ensure their adaptation after being brought from the production farm. In our study while no analgesic substance was given to the control group, the other groups were administered meloxicam (Melosym®, Ipm) (1 mg/kg), ketoprofen (Ketojezik®, Teknovet) (3 mg/kg) and buprenorphine (Simbadol®, Zoetis) (0.025 mg/kg) to the *m. quadriceps* femoris as intramuscularly, respectively (5, 6). The inclusion criteria for this study included male, healthy, 8 months-3 years old and weighing 2.5-5.5 kg rabbits, while the exclusion criteria included having general health problems and old age.

Experimental Study Procedure: All rabbits were weighed and recorded before the study. Preoperatively, the doses of drugs were adjusted according to the weight of the rabbits, bedside monitor probes were connected to the patient and physiological parameters were recorded via the monitor in a quiet and calm environment. T-0 blood was taken from the marginal ear vein and the blood was centrifuged and the serum portion was transferred to another tube and stored at -20°C. Preemptive analgesic agent was applied 30 minutes before the orchiectomy operation. 10 minutes after the analgesic agents were administered, the rabbits were anesthetized by administration of combined medetomidine (0.25 mg/kg) (Domitor®, Pfizer) and ketamine (35 mg/kg) (Ketasol® 10%, Interhas) intramuscularly (7). Following anesthesia, the rabbits were placed on the operating table and the monitor probes were reattached. Physiological parameters were monitored and body temperature was measured rectally with a digital thermometer. T-1 blood was collected 10 minutes after medetomidine-ketamine injection. Scrotum incision and pain scoring were performed 30 minutes after administration of the analgesic agent. While T-2 blood was collected at the end of the orchiectomy operation, T-3, T-4 and T-5 at the 2nd, 4th and 6th hours postoperatively, respectively. At the end of the study, the rabbits were not euthanized and all rabbits were administered Cephalexin (Cephaset®, Alke) after T-5 blood collection. While the control group was planned to be administered meloxicam if they experienced postoperative pain, the other 3 groups were not planned to use rescue analgesia. NK was aware of the group allocation at the different stages of the experiment (during the allocation, the conduct of the experiment, the outcome assessment, and the data analysis).

Monitoring of Rabbits: The red probe was placed in the right armpit, the yellow probe was placed in the left armpit, and the green probe was placed in the sternal region using ultrasound gel. Pulse oximeter was placed on the right/left front paw. In the measurements, heart rate (HR) and respiratory frequency (*fR*) were monitored and recorded with a monitor, body temperature (°C) with a thermometer and SpO_2 (%), with a pulse oximeter placed on the right front paw of the rabbits. Pain scoring was performed by the surgeon during the scrotal skin incision. A pain scoring system was used in the study to asses pain (Score 0, no pain reaction and muscles are relaxed. Score 1, increased muscle tone, slight movement of the lower jaw and hind legs. Score 2, teeth grinding and full movement of the hind legs. Score 3, hind legs stamping hard on the ground and vocalization) (8).

Laboratory Analyses: 0.5-1 mL blood samples were taken from the marginal ear vein of rabbits into Eppendorf tubes. Samples were centrifuged at 1000 rpm, 15 minutes, 2-8°C. The serum stored at -20°C. Rabbit cortisol kit (Elabscience® QuicKey Pro, USA) using the competitive ELISA principle was used to determine serum cortisol levels according to the routine ELISA test principle. An ELISA microplate reader device (Optic Ivymen System® Microplate 2100-C, Spain) was used to read the ELISA test kit.

Statistical Analysis: The numerical data from the study results were tabulated and presented using descriptive statistics. To determine whether the data showed a normal distribution, the Shapiro-Wilk test was applied. Parametric testing techniques were used for

normally distributed data, while non-parametric techniques were applied to non-normally distributed data. Specifically, Kruskal-Wallis ANOVA and Wilcoxon tests were employed to compare data across the preoperative, intraoperative, and postoperative periods.

For the analysis of cortisol level changes, the statistical significance of changes based on group, time, and group-time interactions was assessed using the analysis of variance for repeated measurements. Prior to performing repeated measures ANOVA, the assumptions of normality, homogeneity of variances, and sphericity were checked. The Shapiro-Wilk test confirmed normality, while Mauchly's test of sphericity was used to assess sphericity. If violations of sphericity were detected, the Greenhouse-Geisser correction was applied to adjust the degrees of freedom. Where appropriate, non-parametric alternatives were considered if the assumptions were violated and could not be adequately addressed through corrections.

In all analyses, a significance level of $p<0.05$ was used. The statistical analyses were performed using SPSS 19.0 (IBM, USA). The initial sample size, consisting of 3 groups and 24 animal subjects, was determined using a power test in G*Power (Version 3.1.9.7, F-test, ANOVA).

Results

No preoperative or postoperative complications or deaths were observed in any of the 24 New Zealand White Rabbits used in the study due to anesthesia and surgery. It was determined that the changes in HR did not differ between the groups in terms of each operation measurement time, however, the changes that occurred according to the operation times in each application group were not statistically significant (Table 1). It was determined that *fR* did not change significantly between the groups at each time point, whereas the measurements taken in the preoperative period in the animals administered meloxicam were significantly lower ($p=0.008$) compared to the intraoperative period. However, it was determined that the intraoperative and postoperative measurements in the rabbits in the buprenorphine group showed significant differences with *p* values of 0.020 and 0.015, respectively, compared to the preoperative measurements (Table 2). It was determined that there was no difference in body temperature between the groups at each measurement time. In the measurements made at different times of the operation for each group, it was determined that there were statistically significant changes between the preoperative-postoperative and intraoperative-postoperative periods in the meloxicam group, and there were significant changes between the preoperative-postoperative periods in the buprenorphine group. It was determined that the changes in the intraoperative and postoperative periods were significant in the control group animals (Table 3). Regarding SpO_2 (%) values, it was determined that the ketoprofen and control group measurements were significantly lower than the buprenorphine group measurements in the intraoperative period among the application groups. In the changes that occurred in each group during their own time period, it was determined that the SpO_2 levels of the control group animals were lower in the intraoperative and postoperative periods compared to the preoperative period, while in the ketoprofen-administered group, the preoperative SpO_2 level was significantly higher than the postoperative period. However, it was determined that the SpO_2 values of the animals administered meloxicam in the postoperative period were significantly different from those of the animals administered ketoprofen and buprenorphine (Table 4). It was determined that the changes in cortisol (ng/ml) levels of animals that underwent orchiectomy with analgesic application in the preoperative period were statistically significantly different in terms of time, group and group-time relationships (Table 5, Figure 1).

In this context, it was determined that the increases in cortisol levels in the study group administered ketoprofen after T-1 were significantly higher than in the study group administered meloxicam and buprenorphine and were close to the animals in the control group. In the T-5 time period, it was determined that the highest cortisol level was in the ketoprofen group within the 6th hour postoperatively and that it was significantly higher in the animals in the ketoprofen group than in the meloxicam, buprenorphine and control groups. Considering the 6th hour postoperative cortisol levels, the most effective analgesic agent was determined to be buprenorphine. Based on the pain scores in the rabbit groups used in the study, it was determined that the median value of the pain score of the animals in the control group was 2. While the median value of the pain score was 1 in the meloxicam and ketoprofen group, the median value of the pain score was 0 in the buprenorphine group.

Table 1. Changes in heart rates (min^{-1}) in rabbits during the study for each operation measurement time

Time	Meloxicam ($\bar{x} \pm SE$)	Ketoprofen ($\bar{x} \pm SE$)	Buprenorfine ($\bar{x} \pm SE$)	Control ($\bar{x} \pm SE$)
Preoperative	190.8 ± 15.4	169.0 ± 13.4	193.5 ± 16.5	211.8 ± 21.5
Intraoperative	178.2 ± 8.2	203.8 ± 6.6	181.2 ± 10.6	193.0 ± 17.0
Postoperative	174.8 ± 10.9	197.8 ± 10.0	169.2 ± 8.6	185.3 ± 16.7

SE, Standard Error

Table 2. Changes in respiratory frequencies (min^{-1}) in rabbits during the study for each operation measurement time

Time	Meloxicam (x̄ ± SE)	Ketoprofen (x̄ ± SE)	Buprenorfine (x̄ ± SE)	Control (x̄ ± SE)
Preoperative	29.8 ± 9.5[a]	44.3 ± 11.3	55.3 ± 7.9[a]	34.3 ± 3.1
İntraoperative	54.0 ± 8.3[b]	40.2 ± 4.1	27.2 ± 4.2[b]	44.7 ± 7.3
Postoperative	45.3 ± 4.5	36.5 ± 2.7	27.7 ± 3.9[b]	47.2 ± 10.2

[a,b:] Data shown with different letters in the same column are statistically different. SE, Standard Error

Table 3. Changes in body temperature (°C) in rabbits during the study for each operation measurement time

Time	Meloxicam (x̄ ± SE)	Ketoprofen (x̄ ± SE)	Buprenorfine (x̄ ± SE)	Control (x̄ ± SE)
Preoperative	39.8 ± 0.1[a]	39.3 ± 0.3	39.4 ± 0.1[a]	39.3 ± 0.2
İntraoperative	39.5 ± 0.2[a]	39.4 ± 0.3	39.1 ± 0.2	39.0 ± 0.3[a]
Postoperative	38.9 ± 0.4[b]	38.3 ± 0.3	38.4 ± 0.4[b]	38.1 ± 0.4[b]

[a,b:] Data shown with different letters in the same column are statistically different. SE, Standard Error.

Table 4. Changes in SpO_2 (%) levels in rabbits during the study for each operation measurement time

Time	Meloxicam (x̄ ± SE)	Ketoprofen (x̄ ± SE)	Buprenorfine (x̄ ± SE)	Control (x̄ ± SE)
Preoperative	98.0 ± 0.6	98.0 ± 0.4[a]	99.0 ± 0.4	99.0 ± 0.5[a]
İntraoperative	96.3 ± 2.3	88.8 ± 3.2[xb]	99.0± 0.8[y]	88.7 ± 2.7[xb]
Postoperative	94.5 ± 2.1[x]	85.3 ± 1.8[cy]	95.8 ± 2.7[y]	90.3 ± 2.4[b]

[a,b,c:] Data shown with different letters in the same column are statistically different. x,y: Data shown with different letters in the same row are statistically different. SE, Standard Error.

Table 5. Changes in cortisol (ng/mL) levels in rabbits during the study for each operation measurement time

Time	Meloxicam (x̄ ± SE)	Ketoprofen (x̄ ± SE)	Buprenorfine (x̄ ± SE)	Control (x̄ ± SE)
T-0	43.7 ± 2.3	52.3 ± 2.2	48.6 ± 3.3	49.8 ± 2.6
T-1	47.4 ± 2.7	58.8 ± 4.5	46.1 ± 4.2	57.2 ± 2.0
T-2	55.8 ± 2.6[y]	56.0 ± 2.2[x]	48.2 ± 5.3[y]	58.0 ± 4.3[x]
T-3	52.3 ± 4.5	62.7 ± 4.3	45.1 ± 3.6	51.0 ± 2.9
T-4	58.5 ± 6.8	62.6 ± 4.7	63.5 ± 7.3	53.3 ± 2.1
T-5	48.3 ± 4.4[y]	60.5 ± 2.2[x]	46.7 ± 4.0[y]	49.9 ± 2.5[y]
Time		*p*<0.0001		
Group		*p*<0.0001		
Group-Time		*p*=0.033		

[x,y:] Data shown with different letters in the same line are statistically different. T-0, before analgesia and anesthesia. T-1, 10 minutes after medetomidine-ketamine administration. T-2, after orchiectomy. T-3, 2nd postoperative hour. T-4, 4th postoperative hour. T-5, 6th postoperative hour.

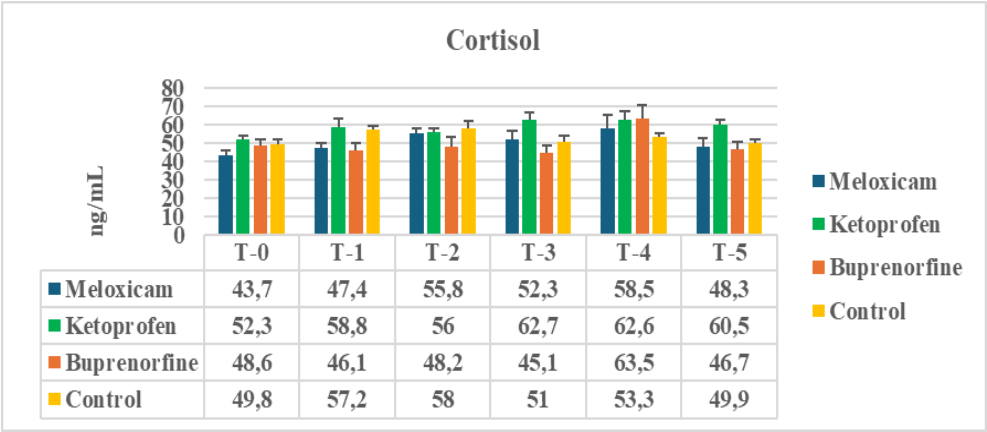

Figure 1. Graph of changes in cortisol (ng/mL) levels in rabbits during the study for each operation measurement time

Discussion

In this study, preemptive analgesic agents, buprenorphine, ketoprofen and meloxicam, were slowly injected into the right *m. quadriceps* femoris of each rabbit before orchiectomy, and then blood was taken at regular intervals to evaluate the analgesic response by looking at various parameters. For this purpose, stress response-related pain score and serum cortisol level were measured. In parallel with our study, metamizole, carprofen and narcotic analgesic fentanyl were used before orchiectomy in 6-month-old male rabbits (8). In parallel with this, our study aimed to be more comprehensive by taking blood from each rabbit in 6 different periods and measuring serum cortisol levels. In rabbits, intramuscular, subcutaneous or oral routes are generally preferred. According to the literature, oral use of meloxicam has mostly been described (9, 10). In our study, the intramuscular route was preferred based on literature data, since oral meloxicam preparations are not widely available in Türkiye and oral drug use is difficult due to the anatomical structure of rabbits. Orchiectomy is a routine surgical operation in male rabbits. Since the perineal region and scrotum are extremely sensitive to pain, incision into the scrotum is the most valid surgical procedure used to reveal the potency of preemptive analgesics. For this reason, orchiectomy was preferred as the surgical procedure for pain scoring in our study (11).

The normal body temperature of a New Zealand rabbit is 38.5–39.5°C (12). In a study in which cows were infused with E. coli lipopolysaccharide and meloxicam was administered, it was concluded that meloxicam has an antipyretic effect in the treatment of acute mastitis in cows (13). We can attribute the decreases in body temperature until the postoperative period in the meloxicam group to medetomidine and ketamine anesthesia. Medetomidine may cause a decrease in body temperature by affecting the thermoregulation center in the hypothalamus (14, 15). Similar results were observed in chinchillas as a result of ketamine medetomidine application (16). In our study, it was also observed that meloxicam caused statistically significant decreases in body temperature. Unlike the meloxicam group, in the ketoprofen group, there was no significant change in body temperature during the study period. In fact, there was an increase in body temperature in this group as the study progressed. In a study comparing the intraoperative effects of 3 different analgesic agents in rabbits, it was reported that carprofen increased body temperature from 38.9°C to 39.1°C intraoperatively (8). In our study, body temperature increased similarly from 39.3°C to 39.4°C during the intraoperative period. Similar effects have been observed since both carprofen and ketoprofen are analgesics from the imidazole group, which are nonsteroidal anti-inflammatory drugs. Defense reactions and increased muscle activity that occur during surgical incision can be considered as another reason for this increase in body temperature. The changes in the buprenorphine group are almost parallel to the data in the meloxicam group, and statistically significant decreases in body temperature are observed before scrotum incision. In a study comparing preemptive buprenorphine and meloxicam in postoperative pain management in female Dutch rabbits, no statistically significant difference was found, and a decrease in anesthesia-related body temperature was observed in all rabbits, but they returned to normal body temperature when they were returned to their cages (17). In parallel with this, in our study the body temperature decreases that occurred due to ketamine and medetomidine returned to normal in the rabbits placed in their cages at the end of the study, and hypothermia and related complications were absent.

According to literature data in rabbits, the physiological value for HR has been reported to be between 180-300 per min, and higher HR is often seen due to increased sympathetic tone due to stress (18). It has been reported that meloxicam has no effect on HR (19). Another study reported that perioperative meloxicam administration reduced adverse postoperative changes on the cardiovascular system without affecting renal function (20). Therefore, this decrease in HR in our study can be attributed to the application of ketamine medetomidine. While medetomidine causes a decrease in HR by causing a decrease in sympathetic tone and an increase in vagal tone, it stimulates peripheral α-2 receptors in the vascular smooth muscles, causing an initial vasoconstriction and then a decrease in HR in response to this (21, 22). Unlike medetomidine, ketamine has a stimulating effect on the circulatory system. Ketamine has a positive inotropic effect on the heart by stimulating β receptors and increases HR (23). Bradycardia resulting from the administration of ketamine and medetomidine has been described in other studies as well as in our study (24). In the ketoprofen group the reason for this increase in HR can be considered as excessive muscle activity and muscle tremors that occur as a result of scrotum incision. This dramatic decrease in HR in the buprenorphine group is due to buprenorphine as well as medetomidine. Because buprenorphine causes a significant sinus bradycardia in all animal species (25). Physiologically, the *fR* value in rabbits varies between 32-100 per min. Both ketamine and medetomidine cause a dose-dependent decrease in *fR* (26, 27). In a study in which ovariohysterectomy was performed in 168 cats, no significant difference in *fR* or HR was observed between the control group and NSAID groups or between different application times of NSAIDs (28). Considering that meloxicam has no effect on *fR*, it is thought that this increase in *fR* may be due to defense reactions that occur as a result of scrotum incision. It can be concluded that the *fR* decreasing to 45.3±4.5 per min in the subsequent postoperative period is an indicator that analgesia is adequate. In the ketoprofen group, intraoperative *fR* per min decreased from 44.3±11.3 to 40.2±4.1, and this value is within physiological limits. Observation of this decrease in *fR* during scrotum incision shows that adequate analgesia was provided in this group of rabbits. In one study, it was observed that ketoprofen, a dual inhibitor of arachidonic acid metabolism, completely prevented the changes in hemodynamics and respiratory functions observed in

animals treated with endotoxin (29). In the buprenorphine group, statistically significant and dramatic decreases in *fR* per min were observed both intraoperatively and postoperatively. This dramatic decrease reveals the potency of buprenorphine, a narcotic analgesic substance. Narcotic analgesics, in addition to providing good analgesia, are known to have typical respiratory depression effects that cause decreases in *fR*. The exact mechanism of buprenorphine's acute toxicity is still not fully understood. Respiratory depression is the suspected etiology of buprenorphine-related deaths. The majority of opioids cause dose-related respiratory depression in experimental models (30).

The SpO_2 level in rabbits physiologically varies between 93-99% (31). In healthy rabbits, initial monitoring values may sometimes not be measured accurately because the rabbit does not sit comfortably before the study. The decrease in SpO_2 value after ketamine-medetomidine application has been demonstrated in many studies (27, 32). In our study intraoperatively SpO_2 level decreased to 96.3±2.3% in the meloxicam group, 88.8±2.3% in the ketoprofen group, and remained at approximately the same level in the buprenorphine group. We can suggest that the increased intraoperative *fR* is responsible for this situation. Because the *fR* increased intraoperatively in the meloxicam group and decreased in the other two groups.

Cortisol level was found to be lowest in the buprenorphine group at all times except T-4 time. This was followed by meloxicam and ketoprofen groups, respectively. Rabbits in the ketoprofen group had the highest serum cortisol levels at all times. One study investigated whether preemptive butarphanol and carprofen administration before ovariohysterectomy had any effects on serum cortisol, C-reactive protein and other vital signs (33). As a result, no statistically significant difference was found in cortisol level at any time interval. In all groups, preoperative serum cortisol levels increased compared to the postoperative period. However, this increase was evident in the control and butorphapol groups. Since the serum cortisol level did not increase significantly in the carprofen group, it was concluded that carprofen was more effective than buturfanol in reducing postoperative stress. In our study, contrary to this study, it was concluded that buprenorphine, a narcotic analgesic, was the most powerful analgesic. In a study on rabbits, metamizole, carprofen and fentanyl were used as preemptive analgesic agents and, contrary to the results of our study, it was found that stronger analgesia was obtained in the carprofen group (8). In our study, the buprenorphine group had the most triple analgesic effect. In our study, the strongest analgesic effect was in the buprenorphine group. When looking at the analgesic effects, it is observed that this situation is also correlated with the serum cortisol level. The lowest increase in serum cortisol level was in the buprenorphine group, followed by the meloxicam and ketoprofen group.

It was concluded that orchiectomy operation in male rabbits could be a suitable study model for preemptive analgesia studies. While an average statistically significant decrease of 0.5°C was observed in preoperative and intraoperative body temperature values measured rectally in rabbits in the meloxicam and buprenorphine groups, a statistically insignificant decrease was observed in the ketoprofen group. During the study, anesthesia-related changes in HR and *fR* were observed in rabbits. However, since these changes are similar to each other, they do not represent statistically significant differences between groups. We can conclude that using SpO_2, *fR* and HR alone in pain scoring is subjective and may cause drawbacks. According to the level of serum cortisol, which is an acute biomarker of pain and pain response, it was concluded that the analgesic agent with the strongest analgesic effect was buprenorphine and the analgesic agent with the weakest analgesic effect was ketoprofen in the doses and administration routes specified in the study during orchiectomy operations in rabbits.

References

1. Johnston MS. Clinical approaches to analgesia in ferrets and rabbits. Seminars in Avian and Exotic Pet Medicine 2005; 14(4): 229-235.
2. Keown AJ, Farnworth MJ, Adams NJ. Attitudes towards perception and management of pain in rabbits and guinea pigs by a sample of veterinarians in New Zealand. New Zeland Veterinary Journal 2011; 59(6): 305-310.
3. Rooney NJ, Blackwell EJ, Mullan SM, et al. The current state of welfare, housing and husbandry of the English pet rabbit population. BMC Res Notes 2014; 7: 1-13.
4. Kohn DF, Martin TE, Foley PL, et al. Guidelines for the assessment and management of pain in rodents and rabbits. J Am Assoc Lab Anim Sci 2007; 46(2): 97-108.
5. Meredith A. BSAVA Small Animal Formulary. In: Meredith A. (Editör). Part B Exotic Pets. BSAVA-British Small Animal Veterinary Association 2016.
6. Vennen KM, Mitchell MA. Rabbits. In: Manual of exotic pet practice. WB Saunders 2009: 375-405.
7. Lipman NS, Marini RP, Flecknell PA. Anesthesia and Analgesia in Rabbits. In: Kohn DF, Wixson SK, White WJ, Benson GJ. (Editors). Anesthesia and analgesia in laboratory animals. Academic Press, California, U.S.A. 1997: 205-232.
8. Clemm A. Vergleichsuntersuchungen zur intraoperativen analgetischen Wirksamkeit von Metamizol, Carprofen und Fentanyl bei der Orchiektomie des Kaninchens. Doctoral thesis, Ludwig, Maximilians: Universität München, 2008.
9. Carpenter JW, Pollock CG, Koch DE, Hunter RP. Single and multiple-dose pharmacokinetics of meloxicam after oral administration to the rabbit (Oryctolagus cuniculus). J Zoo Wildl Med 2009; 40(4): 601-606.

10. Leach MC, Allweiler S, Richardson C, et al. Behavioural effects of ovariohysterectomy and oral administration of meloxicam in laboratory housed rabbits. Research in veterinary science 2009; 87(2): 336-347.

11. Henke J, Erhardt W. Das Problem Schmerz. In: Henke J, Erhardt W. (Editors). Schmerzmanagement bei Klein und Heimtieren. Enke Verlag, Stuttgart: 2001; 1-6.

12. Ruckebusch Y, Phaneuf LP, Dunlop R. Physiology of small and large animals. Dekker, Philadelphia, 1991.

13. Fitzpatrick CE, Chapinal N, Petersson-Wolfe CS, et al. The effect of meloxicam on pain sensitivity, rumination time, and clinical signs in dairy cows with endotoxininduced clinical mastitis. J Dairy Sci, 2013; 96(5): 2847-2856.

14. Blum JR, Daunt DA, Hamm TE, et al. Effects of medetomidine and medetomidine plus ketamine in rabbits (abstract). Proc 4th Int Congr Vet Anaesth Utrecht, 1991; 86.

15. Heavner JE. Pharmacology of analgesics. In: Anesthesia and analgesia in laboratory animals. Academic Press, 1997: 43-56.

16. Röltgen I, Zur Anästhesie beim Chinchilla (Chinchilla lanigera) mit Midazolam, Medetomidin und Fentanyl und ihrer vollständigen Antagonisierung mit Flumazenil, Atipamezol und Naloxon im Vergleich zur Anästhesie mit Xylazin/Ketamin und Medetomidin/Ketamin. Hieronymus; 2002.

17. Cooper CS, Metcalf-Pate KA, Barat CE, et al. Comparison of side effects between buprenorphine and meloxicam used postoperatively in Dutch belted rabbits (Oryctolagus cuniculus). J Am Assoc Lab Anim Sci 2009; 48(3): 279-285.

18. Sohn J, Couto MA. Anatomy, Physiology, and Behavior. In: Suckow MA, Stevens KA, Wilson RP. (Editors). The Laboratory Rabbit, Guinea Pig, Hamster, and Other Rodents. Elsevier, Amsterdam; 2012; 195-215.

19. Avellaneda C, Gomez A, Martos F, et al. The effect of a single intravenous dose of metamizol 2 g, ketorolac 30 mg and propacetamol 1 g on haemodynamic parameters and postoperative pain after heart surgery. Eur J Anaesthesiol 2000; 17(2): 85-90.

20. Gates BJ, Nguyen TT, Setter SM, Davies NM. Meloxicam: A reappraisal of pharmacokinetics, efficacy and safety. Expert Opin Pharmacother 2005; 6(12): 2117-2140.

21. Vainio O, Palmu L. Cardiovascular and respiratory effects of medetomidine in dogs and influence of anticholinergics. Acta Vet Scand 1989; 30: 401-408.

22. Sinclair MD. A review of the physiological effects of α- 2 agonists related to the clinical use of medetomidine in small animal practice. Can Vet J 2003; 44(11): 885.

23. Frey HH, Schulz R, Werner E. Pharmakologie des zentralen Nervensystems. In: Frey HH, Löscher W. (Editors). Lehrbuch der Pharmakologie und Toxikologie für die Veterinärmedizin. Springer, Berlin 1996; 139-202.

24. Adams HA, Werner C. Vom Razemat zum Eutomer (S)-Ketamin: Renaissance einer Substanz? Der Anaesthesist 1997; 46: 1026-1042.

25. Freye E, Hartung E. Wirkweise der Opioide. In: Freye E, Hartung E. (Editors). Opioide und ihre Antagonisten in der Anästhesiologie. Perimed Fachbuch-Verlags GmbH. 1984; 20-52.

26. Paddleford RR, Erhardt W. Allgemeinanästhesie. In: Erhardt W. (Editör). Anästhesie bei Kleintieren. Schattauer, Stuttgart 1992; 37-83.

27. Blum JR, Daunt DA, Hamm TE, et al. Cardiorespiratory effects of medetomidine in rabbits. 1992; 2(1): 158.

28. Höglund OV, Dyall B, Gräsman V, et al. Effect of non-steroidal antiinflammatory drugs on postoperative respiratory and heart rate in cats subjected to ovariohysterectomy. J Feline Med Surg 2018; 20(10): 980-984.

29. Sigurdsson GH, Youssef HAF, Banic A. Effects of ketoprofen on respiratory and circulatory changes in endotoxic shock. Intensive Care Med 1993; 19: 333-339.

30. Cowan A, Doxey JC, Harry EJR. The animal pharmacology of buprenorphine, an oripavine analgesic agent. Br J Pharmacol 1977; 60(4): 547.

31. Haberstroh J, Henke JK. In: Erhardt W, Henke JK, Haberstroh J. (Editors). Anaesthesie & Analgesie beim Klein- und Heimtier. Schattauer, Stuttgart 2004; 629-640.

32. Wright M. Pharmacologic effects of ketamine and its use in veterinary medicine. J Am Vet Med Assoc 1982; 180(12): 1462-1471.

33. Er İ. Effects of preemptive butorphanol and carprofen applications on cortisol, c-reactive protein and vital signs in cats undergoing ovariohysterectomy. Master's Thesis, Aydın Adnan Menderes University, Health Sciences Institute, 2019.