Iranian Journal of Veterinary Surgery

ORIGINAL ARTICLE

Intraosseous Propofol versus Isoflurane Anesthesia in Rabbits: Comparative Analysis of Clinical Parameters, Induction Quality, and Recovery Outcomes

Armin Motamedi, Mahdi Farid ✉, Firoozeh Saghaei

Department of Veterinary Medicine, ShK.C., Islamic Azad University, Shahrekord, Iran.

ARTICLE INFO

Article History:

Received: 14 December 2025
Revised: 22 April 2026
Accepted: 29 April 2026

Keywords:

Anesthesia
Rabbit
Isoflurane
Propofol

ABSTRACT

This study compared intraosseous (IO) propofol with inhalational isoflurane anesthesia in 12 healthy male New Zealand White rabbits, evaluating clinical performance, physiological stability, and factors predicting recovery. Animals were randomly assigned to receive either intraosseous propofol or isoflurane for a 30-minute anesthetic period, and cardiopulmonary variables were recorded every 5 minutes. Loss of pedal and palpebral reflexes occurred faster with propofol, with mean times of 1.15 minutes and 0.47 minutes, compared with 2.03 minutes and 1.02 minutes with isoflurane ($p < 0.05$). The total duration of anesthesia was longer with propofol (36.33 minutes versus 33.58 minutes; $p < 0.05$), as was recovery time (6.92 minutes versus 5.00 minutes; $p < 0.05$). Anesthesia and recovery quality scores showed no significant differences ($p > 0.05$). Propofol produced higher early post-induction heart rates ($p < 0.05$) and greater temperature fluctuations, whereas isoflurane maintained higher oxygen saturation throughout anesthesia ($p < 0.05$). Predictive modelling showed that changes in oxygen saturation and rectal temperature independently predicted recovery time ($p < 0.05$). Logistic regression classified recovery quality with 85.4 percent accuracy, identifying changes in heart rate, respiratory rate, and oxygen saturation as significant predictors (all $p < 0.05$). Decision tree analysis achieved 88.9 percent accuracy and ranked changes in oxygen saturation and rectal temperature as the strongest determinants of recovery quality. Overall, intraosseous propofol provided rapid induction and acceptable stability but required closer support to maintain body temperature and oxygenation. Isoflurane offered better control of oxygen saturation and temperature. The modelling results highlight the importance of maintaining adequate oxygen saturation, body temperature, and respiratory stability to optimize recovery from anesthesia in rabbits.

Introduction

The rising popularity of pet rabbits and their significant role in biomedical research have driven the demand for safe and effective anesthesia in this species. Rabbits are the third most frequently anesthetized companion animals after dogs and cats; however, their peri-anesthetic morbidity and mortality rates are reported to be up to seven times higher than in canine and feline patients.[1,2] Risk factors include unique anatomical constraints such as a narrow oral cavity, deep pharynx, large tongue, and delicate airway combined with a high metabolic rate and pronounced vagal reflexes, predisposing them to rapid cardiopulmonary compromise under anesthesia.[3,4]

✉ Corresponding author. Email: mehdifareed@yahoo.com

https://doi.org/10.30500/ivsa.2026.566141.1478

Among inhalational agents, isoflurane remains a mainstay due to its rapid titratability, stable recovery profile, and minimal biotransformation. However, its safe administration often requires orotracheal intubation, which in rabbits can be technically challenging and carries risks of laryngeal trauma, laryngospasm, and tracheal injury.[2,5] Face-mask delivery, while avoiding intubation, may result in inconsistent anesthetic depth, hypoventilation, and environmental contamination with waste anesthetic gases.[6] Intravenous (IV) administration of anesthetic agents such as propofol allows for precise control, rapid onset and smooth recovery.[6] Yet establishing peripheral venous access in rabbits particularly in emergency settings involving hypovolemia or vascular collapse can be logistically difficult and delay induction.[7,8] Intraosseous (IO) catheterization offers a rapid and reliable alternative. By delivering drugs directly into the medullary cavity, IO access achieves pharmacokinetics comparable to IV infusion.[9,10] In both human and veterinary critical care, this technique has been used for decades for fluid resuscitation, analgesia, and drug administration when venous catheterization fails.[11] Evidence for IO delivery of propofol in rabbits suggests effective induction and maintenance with minimal hemodynamic instability,[3,9] but comparative trials with inhalational anesthesia are scarce. Given the practical limitations of inhalational protocols in this species, particularly in cases where airway manipulation or venous catheterization are contraindicated, IO delivery of propofol may represent a clinically valuable alternative. This study aims to provide a head-to-head comparison of IO propofol and inhalational isoflurane anesthesia in healthy rabbits, assessing induction and recovery times, cardiorespiratory stability, oxygenation, thermal regulation to evaluate IO propofol as a potential substitute when conventional inhalational techniques are challenged.

Materials and Methods

Twelve healthy male New Zealand white rabbits with average weight of 2.5 ± 0.2 kilograms (kg) and aged 1 year were included in the study. Ethical approval was obtained from the research ethics committees of a veterinary research facility (approval ID: IR.IAU.SHK.REC.1402.141). They were maintained in standard temperature conditions ranging from 25 to 30 degrees Celsius and kept under a 12-hour light and 12-hour dark cycle. Animals underwent a complete physical examination before anesthesia. Inclusion criteria compromised clinically normal status on pre-anesthetic examinations, normal hematological and biochemical parameters, and absence of any illness. Exclusion criteria included evidence of systemic diseases, abnormal pre-anesthetic findings, poor body condition and behavioral issues impairing safe handling. Subjects were randomly allocated to two equal groups (n = 6) using a computer-generated simple randomization list prepared by a researcher not involved in the experiment. The sample size calculation considered a mean heart rate difference of 10 beats per minute between groups, a standard deviation of 5 beats per minute, $\alpha = 0.05$ (two-tailed), and $\beta = 0.20$ (80% power), yielding a minimum of five animals per group. Given the ethical and logistic constraints associated with animal use, six animals per group were selected. Upon completion of the experiment and confirmation of the animals' continued good health, all rabbits were returned to the laboratory animals housing facility. Prior to anesthesia, both groups of rabbits were fasted for 2 hours and underwent a clinical examination to confirm their general health status. In the first group, which received IO anesthesia with propofol, vascular access was established via the proximal end of the tibia. The craniomedial surface at the proximal tibia metaphysis was clipped and aseptically prepared with povidone–iodine solution.[7] Local anesthesia was achieved by infiltrating 0.5 ml of 1% lidocaine hydrochloride (Bayer Aflak, Lorestan, Iran) into the skin and periosteum at the intended insertion site.[9] A 19-gauge needle was inserted into the medullary cavity at an angle of approximately 30° to the longitudinal axis of the bone, with cortical penetration indicated by a sudden decrease in resistance. Proper placement was confirmed by aspiration of marrow and free infusion of fluids without evidence of subcutaneous extravasation. The needle was then flushed with heparinized normal saline (10 IU/ml) and secured in place. Adequate analgesia was confirmed before needle insertion by absence of withdrawal response to gentle pressure on the site by using hemostat forceps. Anesthesia was induced with propofol 1% with dosage of 12.5 mg/kg (B. Braun, Melsungen AG, Germany) administered over a 10-second period via an automatic infusion pump (SP-500; JMS Co. Ltd., Japan). Following induction, anesthesia was maintained with a continuous propofol infusion at 1 mg /kg/min for 30 minutes using the same pump,[9] Propofol infusion was discontinued after 30 minutes. In the second group, anesthesia was induced with isoflurane (Terrell; Pennsylvania, USA) in oxygen, delivered via face mask. Following loss of the gag and righting reflexes, orotracheal intubation was performed using an appropriately sized endotracheal tube connected to an anesthesia machine (SA-2; Dräger, Lübeck, Germany). Anesthesia was maintained with isoflurane. Isoflurane was administered at concentrations ranging from 1 to 4% along with oxygen. After 30 minutes, delivery of the inhalant anesthetic was discontinued. Animals were disconnected from the anesthesia circuit once gag reflexes had returned. To minimize aversive stimuli, animals received pre-oxygenation for 2 minutes before

mask placement, and induction was performed gradually while monitoring for signs of distress. In both groups, heart rate (HR) and respiratory rate (RR) were monitored using a stethoscope (Cardiology IV, Littmann; 3M, USA), rectal temperature was recorded with a digital thermometer (TK250, Accumed; Rossmax, Switzerland), and oxygen saturation (SpO_2) was assessed with a multiparameter vital signs monitoring device (PM-7000VET; Zoncare, China). Measurements were obtained at five-minute intervals throughout the anesthetic period. The duration of anesthesia induction was measured from the start of drug injection to the loss of the righting reflex. The total anesthesia time was noted from the loss of the righting reflex until its return, and recovery time was measured from the cessation of anesthesia to the return of the righting reflex, all expressed in seconds.[9]

Anesthesia quality was evaluated based on several parameters: response to painful stimuli, maintenance of sternal positioning, and timing of reflex losses. The scoring for anesthesia quality was as follows:[9] Score 0: Strong response to stimuli, Score 1: Moderate response with sternal positioning, Score 2: Weak response and failure to maintain sternal position, Score 3: Deep general anesthesia.

Recovery quality was also scored based on the animal's behavior and reflexes during the recovery phase:[9] Score 0: Calm, appropriate behavior with no severe physical movements, Score 1: Mildly aggressive, significant movements, Score 2: Severe movements, Score 3: Lack of response.

Data distribution was assessed using the Shapiro–Wilk test. Continuous variables with normal distribution were compared between groups using independent-samples *t*-tests, while non-normally distributed data were analyzed using the Mann–Whitney *U* test. Paired comparisons within groups were performed using paired *t*-tests or Wilcoxon signed-rank tests, as appropriate. Reflex loss times, anesthesia duration, and recovery metrics were summarized as mean ± SD or median (range). Repeated measures of physiological parameters (HR, RR, rectal temperature, SpO_2) were analyzed using two-way repeated-measures ANOVA with Bonferroni post-hoc adjustments for multiple comparisons. Effect sizes were calculated as Cohen's *d* for parametric data and rank-biserial correlation for non-parametric data. Predictive analyses were conducted to identify determinants of recovery outcomes. Multiple linear regression (forward stepwise) was used to predict recovery time, reporting unstandardized coefficients (β), adjusted R^2, and significance values. Binary logistic regression assessed predictors of recovery quality, with odds ratios (OR) and 95% confidence intervals. A decision tree model (CART algorithm) identified the most influential variables by Gini importance. Model accuracy, sensitivity, and specificity were calculated from confusion matrices. All analyses used $p < 0.05$ (two-tailed) as the threshold for statistical significance. Data analyses were performed in SPSS Statistics (version 29, IBM Corp., USA) and GraphPad Prism (version 10, GraphPad Software, USA).

Results

Intraosseous propofol administration (Group 1) produced a significantly faster loss of pedal reflex (1.15 ± 0.25 min) compared with isoflurane (Group 2) (2.03 ± 0.36 min; $p < 0.05$, Figure 1). Similarly, the time to loss of palpebral reflex was shorter in Group 1 (0.47 ± 0.02 min) compared with Group 2 (1.02 ± 0.21 min; $p < 0.05$, Figure 1). The total anesthesia duration was significantly longer in the propofol group (36.33 ± 0.96 min) than in the isoflurane group (33.58 ± 0.85 min; $p < 0.05$, Figure 1). Recovery time was significantly longer for Group 1 (6.92 ± 1.11 min) compared with Group 2 (5.00 ± 0.71 min; $p < 0.05$, Figure 1). Anesthesia quality scores were uniformly high in both groups (median = 3, range = 3–3; $p > 0.05$, Figure 1). Recovery quality was smooth in all animals and showed no statistically significant difference between Group 1 (median = 0, range = 0–1) and Group 2 (median = 0, range = 0–0) ($p > 0.05$, Figure 1). Physiological monitoring revealed that propofol was associated with significantly higher HR at 5 minutes, 10 minutes, and 25 minutes' post induction ($p < 0.05$), compared with isoflurane (Figure 2). Respiratory rate was significantly different between groups at 0, 5, 10, 15, 20, 25, and 30 minutes ($p < 0.05$, Figure 3). Rectal temperature differed significantly between groups at all-time points except at 10 minutes ($p < 0.05$), with greater fluctuations in Group 1 (Figure 4). SpO_2 remained higher in the isoflurane group across all times, with p values between 0.0015 and 0.0046 (Figure 5). Predictive modeling analyses further illuminated recovery determinants. A multiple linear regression model (adjusted $R^2 = 0.81$; $p < 0.001$) identified ΔSpO_2 (β = –0.64, $p < 0.001$) and Δrectal temperature (β = –0.43, $p = 0.004$) as the strongest independent predictors of recovery time, indicating that greater declines in oxygen saturation or body temperature were associated with delayed recovery. Multinomial logistic regression classified recovery quality with 85.4% overall accuracy, 83.3% sensitivity, and 87.5% specificity; significant predictors included ΔHR (OR = 1.25, $p = 0.018$), ΔRR (OR = 0.87, $p = 0.034$), and ΔSpO_2 (OR = 0.79, $p = 0.006$). Decision tree analysis achieved 88.9% accuracy, ranking ΔSpO_2 (Gini importance = 0.41). Collectively, these findings underscore the critical role of maintaining oxygenation, thermal stability, and respiratory function for optimal post-anesthetic recovery.

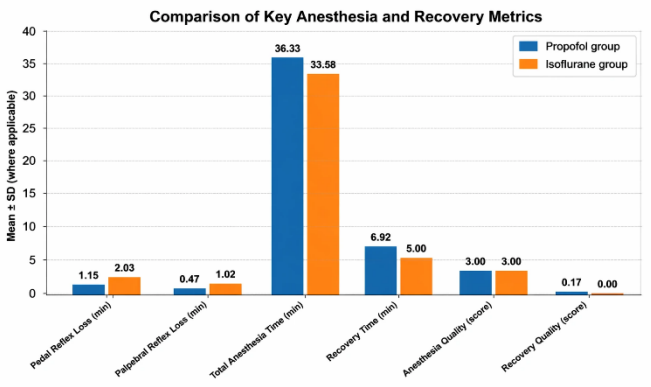

Figure 1. Comparative bar chart showing key anesthesia and recovery metrics for intraosseous propofol (blue) and inhalational isoflurane (orange) groups in rabbits. Values represent group means; for quality scores, medians are shown.

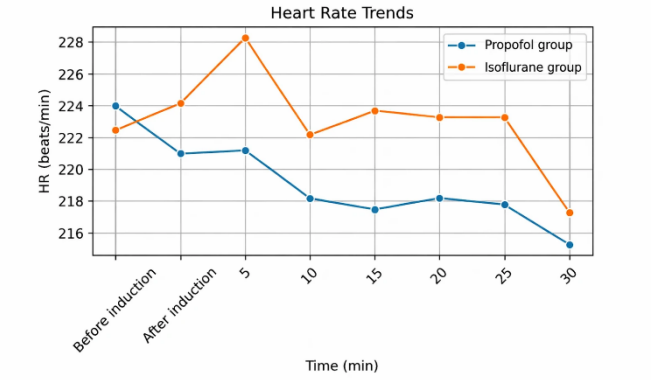

Figure 2. Line chart showing heart rate trends (beats per minute) over time during anesthesia in rabbits receiving intraosseous propofol versus inhalational isoflurane. Markers represent mean values at each time point, with physiological stability assessed via repeated measures analysis.

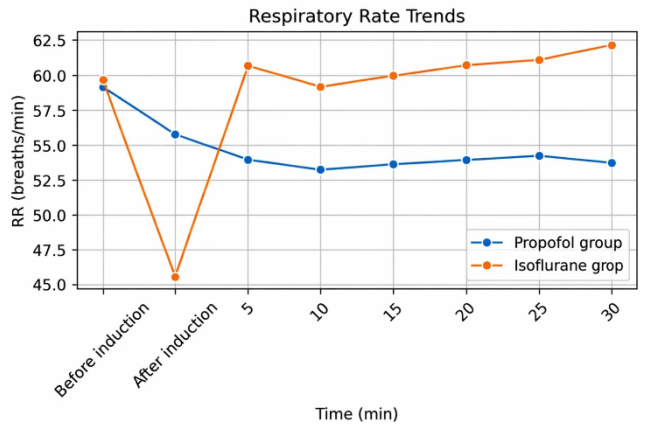

Figure 3. Line chart depicting respiratory rate trends (breaths per minute) over time for both anesthetic protocols. The data indicate differences in respiratory depression patterns between treatments.

Discussion

This study provides a comparison between IO administration of propofol and inhalational anesthesia with isoflurane in healthy rabbits, focusing on induction and recovery characteristics, cardiopulmonary trends, and thermal regulations. The rapid induction with IO propofol observed in our study is in line with previous

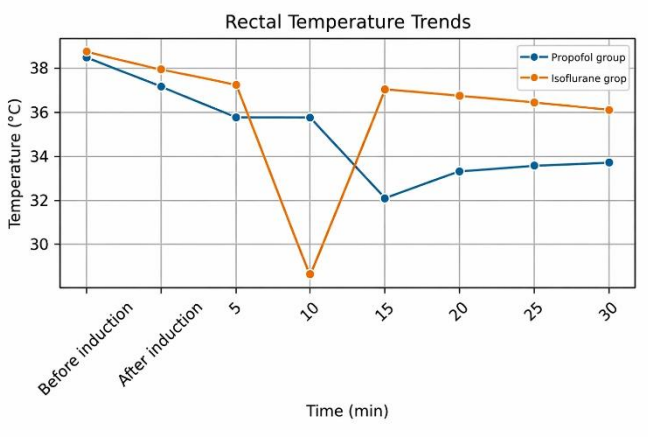

Figure 4. Line chart illustrating rectal temperature changes (°C) during anesthesia maintenance. Trends reveal the degree of thermoregulatory impact of each anesthetic agent.

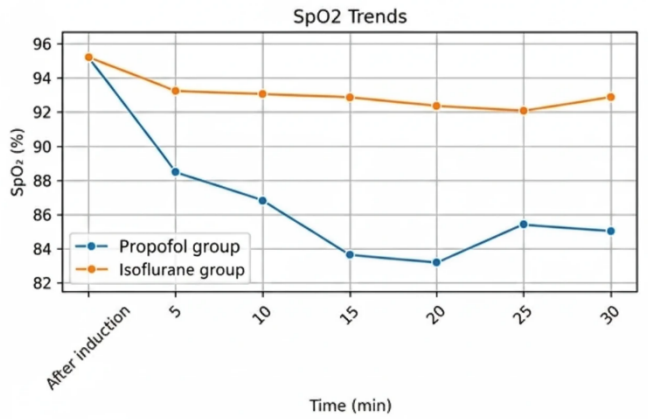

Figure 5. Line chart representing arterial oxygen saturation (SpO_2, %) over time for each anesthetic group, indicating oxygenation efficiency during the anesthetic period.

reports indicating similar pharmacokinetics for IO and IV routes. This similarity in absorption kinetics is attributed to the direct access of the IO routes to the central circulation, bypassing the slower absorption phase often seen with other non-intravenous parenteral routes.[7,9] Conversely, isoflurane induction was predictably slower. This reflects the fundamental principle of inhalation anesthesia, which relies on the uptake of the anesthetic agent into the lungs, diffusion into the bloodstream and subsequent distribution to the brain to achieve central nervous system depression. The time required to achieve an adequate alveolar concentration via mask delivery is influenced by factors such as respiratory rate, tidal volume, and solubility of the agent in blood and tissues.[2,6] In terms of recovery, isoflurane demonstrated significantly shorter recovery times. This is a well-established characteristic of isoflurane, attributed to its low blood-gas partition coefficient. A low partition coefficient signifies that the agent has low solubility in blood, allowing for rapid elimination from the body once the anesthetic vapor is discontinued.[2,12] Clinically, the comparable anesthesia quality scores between the two groups confirm that both protocols, when administered by experienced personnel, can provide stable surgical

planes in rabbits. However, the observed differences in recovery duration are crucial for case selection. For procedures requiring a rapid return to ambulation or when minimizing anesthetic exposure is paramount, isoflurane might be preferred. Conversely, if rapid induction is the primary concern, IO propofol emerges as a viable option.[13] Our data showed transiently higher HR and RR with IO propofol early in anesthesia. This observation aligns with the understanding that injectable anesthetic protocols, can sometimes lead to a preservation of sympathetic tone.[14] In contrast, isoflurane's cardiopulmonary profile was characterized by more stable HR and RR. This aligns with its well-documented properties of myocardial stability, meaning it generally causes less direct myocardial depression.[15] The rectal temperature lability observed in the propofol group corroborates earlier findings that injectable anesthesia, in general, can increase the risk of hypothermia.[2] This increased risk is multifactorial, stemming from several mechanisms: reduced metabolic rate due to anesthetic-induced central nervous system depression, peripheral vasodilation that can lead to increased heat loss, and potentially impaired thermoregulatory responses. Isoflurane, in our study, was associated with better thermal stability. This advantage is likely due to a combination of factors. The use of supplemental oxygen, administered via a mask or chamber, can help maintain core body temperature by reducing the rate of heat loss through respiration and by ensuring adequate oxygenation for cellular metabolism.[2] Furthermore, the ability to adjust the isoflurane vaporizer setting allows for precise control over the depth of anesthesia, and consequently, over the degree of metabolic depression and peripheral vasodilation, thereby facilitating better thermoregulation.[6] These findings are consistent with general principles of anesthesia and recent guidelines for rabbit anesthesia, which emphasize the importance of maintaining normothermia.[1,16]

In clinical practice, IO propofol should be seriously considered as a primary anesthetic option when IV access is not readily achievable. This scenario is common in emergency situations, such as trauma cases or acute respiratory distress, where venous catheterization may be difficult, time-consuming, or even contraindicated. Furthermore, its rapid induction makes it an attractive choice for fragile or highly stressed patients where prolonged restraint for venous access might induce undue physiological stress and compromise their condition.[11,17] However, the clinical utility of IO propofol is contingent upon a thorough understanding and proactive management of its associated physiological trade-offs. Specifically, veterinary professionals must pay meticulous attention to perioperative oxygenation and thermal support. Close monitoring of cardiovascular and respiratory parameters is also crucial to detect and manage any early signs of instability. Conversely, isoflurane remains a preferred anesthetic agent for procedures requiring predictable recovery characteristics and superior physiological stability, particularly in extended or delicate surgical interventions. Its ability to maintain better thermal homeostasis and oxygenation, coupled with its readily titratable nature for precise anesthetic depth control, makes it a safer choice for complex or prolonged procedures where a wider margin of physiological support is desirable. The faster and more predictable recovery associated with isoflurane can also be advantageous in situations where early ambulation or extubation is a critical outcome. Ultimately, the choice between IO propofol and isoflurane should be guided by a comprehensive assessment of the individual patient's health status, the nature of the procedure, the available resources, and the expertise of the veterinary team. A balanced approach, considering both the benefits and risks of each agent, is essential for optimizing anesthetic outcomes in rabbits. Both IO propofol and isoflurane can provide clinically acceptable anesthesia in healthy rabbits, each offering distinct advantages and disadvantages. Isoflurane generally offers superior recovery time and physiological stability, particularly concerning thermal regulation and oxygenation, making it a reliable choice for a broad spectrum of procedures. Conversely, IO propofol remains a viable and often indispensable alternative when inhalational anesthesia is impractical, inaccessible, or undesirable, especially in emergency settings or when rapid induction is a priority. However, its use necessitates a commitment to providing adequate supportive care, including diligent thermal support and oxygen supplementation, to mitigate potential complications.

Acknowledgment

The authors would like to acknowledge the respectful staff of Giv veterinary hospital in Shahrekord, Iran, for their support and contributions to this study.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Brodbelt D. Perioperative mortality in small animal anesthesia. *Veterinary Journal*. 2008; 182: 152-161. doi: 10.1016/j.tvjl.2008.06.011
2. Lamont L, Grimm K. Veterinary anesthesia and analgesia: Lumb and Jones. 6th edn. John Wiley & sons, New Jersey, USA, 2024.
3. Sarrafzadeh-Rezaei F, Dalir-Naghadeh B, Hassanpour H. Induction of general anesthesia with intraoseous injection of

thiopental in rabbits. *Iranian Journal of Veterinary Research*. 2008; 24: 227-232. doi: 10.22099/ijvr.2008.569
4. Gardhouse F, Sanchez A. Rabbit sedation and anesthesia. *Sedation and Anesthesia in Zoological Companion Animals*. 2022; 25: 181-210. doi: 10.1016/j.cvex.2021.08.012
5. Fusco A, Douglas H, Barba A, Hopster K, Stefanovski D, Sinder B, Cahill PJ, Snyder B, Schaer TP. V-Gel guided endotracheal intubation in rabbits. *Frontiers in Veterinary Science*. 2021; 8. doi: 10.3389/fvets.2021.684624
6. Miller RD. Miller's anesthesia. 5th edn. Elsevier, Amsterdam, Netherlands, 2015.
7. Kennedy C R, Gladden J N, Rozanski E A. Comparison of 3 intraosseous catheter sites and methods of determining placement success in cadaver rabbits. *Canadian Journal of Veterinary Research*. 2020; 84: 33-36.
8. Bersanetti G, Martorelli M. Anesthesia in rabbits. *Veterinaria (Cremona)*. 2021; 35: 221-230.
9. Mazaheri-Khameneh R, Sarrafzadeh F, Asri-Rezaei S, Dalir-Naghadeh, B. Evaluation of clinical and paraclinical effects of intraosseous vs intravenous administration of propofol on general anesthesia in rabbits. *Veterinary Research Forum*. 2012; 3: 103-109.
10. Kamiloglu A, Atalan G, Kamiloglu NN. Comparison of intraosseous and intramuscular drug administration for induction of anaesthesia in domestic pigeons. *Research Journal of Veterinary Sciences*. 2008; 85: 171-175. doi: 10.1016/j.rvsc.2007.09.002
11. Marjani M, Mehrvar A. Comparison of intravenous and intraosseous anesthesia in animal models. *Journal of Iranian Society of Anesthesiology and Intensive Care*. 2012; 34: 51-57. [Persian]
12. Martin-Cancho M F, Lima RJ, Luis L, Crisostomo V, Carrasco-Jimenez MS, Uson-Gargallo, J. Relationship of bispectral index values, haemodynamic changes and recovery times during sevoflurane or propofol anaesthesia in rabbits. *Laboratory Animals*. 2006; 40: 28-42. doi: 10.1258/002367706775404462
13. Machin KL, Caulket NA. Evaluation of isoflurane and propofol anesthesia for intraabdominal transmitter placement in nesting female canvasback ducks. *Journal of Wildlife Diseases*. 2000; 36(2): 324-334. doi: 10.7589/0090-3558-36.2.324
14. Flecknell P. Laboratory animal anesthesia. 4th edn. Elsevier, Amsterdam, Netherlands, 2015.
15. Wenger S. Anesthesia and analgesia in rabbits and rodents. *Journal of Exotic Pet Medicine*. 2012; 21: 7-16. doi: 10.1053/j.jepm.2011.11.010
16. Bateman L, Ludders JW, Gleed RD. Comparison between facemask and laryngeal mask airway in rabbits during isoflurane anesthesia. *Veterinary Anesthesia and Analgesia*. 2005; 32: 280-288. doi: 10.1111/j.1467-2995.2005. 00169.x
17. Daneshi M. Clinical comparison between intraosseous and intravenous anesthesia by a combination of ketamine–xylazine in dog. *Journal of Clinical Research of Large Animals*. 2007; 1: 7-11. [Persian]