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SHORT COMMUNICATION

Comparison of clinical and paraclinical effects of intraosseous propofol versus inhalational isoflurane anesthesia in rabbits

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ABSTRACT. This study aimed to compare the clinical and paraclinical effects of inhalational isoflurane anesthesia with intraosseous propofol anesthesia in rabbits. Twelve healthy white rabbits (2 kg, 12 months old) were randomly allocated to two groups (n = 6). Group 1 received intraosseous propofol, and Group 2 underwent induction and maintenance with isoflurane for 30 min. Heart rate, respiratory rate, rectal temperature, and oxygen saturation were recorded every 5 min during anesthesia. Hematological and serum biochemical parameters were evaluated pre-and post-anesthesia. Hematological parameters and biochemical indices were measured in each group pre- and post-anesthesia, and changes in these variables were compared between the two groups. Heart rate remained comparable between the groups, except at 5, 10, and 25 min post-induction. The respiratory rate differed significantly between the groups throughout the duration of anesthesia in both groups ($P < 0.05$). Hematocrit, hemoglobin, and red and white blood cell counts decreased post-anesthesia, with greater reductions in hematocrit and hemoglobin in the isoflurane group ($P < 0.05$). Serum activities of alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) significantly declined in both groups ($P < 0.05$). Intraosseous propofol provided rapid induction, stable cardiopulmonary parameters, and acceptable biochemical safety, whereas isoflurane offered superior oxygenation. These findings suggest that intraosseous propofol administration is a practical alternative when venous catheterization or airway intubation is difficult, especially in emergency situations.

Keywords: biochemistry, hematology, pharmacodynamics, pharmacokinetics

INTRODUCTION

The increasing popularity of companion rabbits has led to a higher demand for surgical procedures, making them the third most frequently anesthetized pet species after dogs and cats. However, the risk of anesthesia-related morbidity and mortality in rabbits is up to seven times greater than that in canine and feline patients, largely due to species-specific anatomical and physiological characteristics (Brodbelt, 2009; Lamont & Grimm, 2024). Successful anesthetic management depends not only on the choice of pharmacological agents for sedation, induction, and maintenance, but also on the route of administration, which must be tailored to the patient's condition and surgical needs (Sarrafzadeh-Rezaei *et al*., 2008; Gadhouse & Sanchez, 2022). Inhalational agents, such as isoflurane, are favored in small mammals for their rapid induction, predictable depth, and short recovery; however, their delivery requires endotracheal intubation or face masks (Lamont & Grimm, 2024; Gadhouse & Sanchez, 2022). Both methods are challenging in rabbits because of their small oral cavity, narrow airway, and sensitivity to laryngeal manipulation, with a risk of laryngospasm, tracheal injury, and stress (Fusco *et al*., 2021). Establishing peripheral venous access for intravenous drug delivery can be technically difficult in this species, particularly in emergencies or in compromised patients (Bersanetti & Martorelli, 2021). Propofol, a short-acting alkylphenol anesthetic, provides smooth induction and recovery when administered intravenously (Lamont & Grimm, 2024; Kennedy *et al*., 2020). Intraosseous administration by directly accessing the medullary cavity achieves pharmacokinetics comparable to intravenous delivery and offers a practical alternative when venous catheterization is not feasible. Although intraosseous access has long been used in emergency medicine for fluid and drug delivery, studies on its application for anesthetic induction and maintenance in rabbits are limited (Sarrafzadeh-Rezaei *et al*., 2008; Mazaheri-Khameneh *et al*., 2012). This study compared the clinical, hematological, and biochemical effects of intraosseous propofol with those of isoflurane inhalational anesthesia in healthy rabbits, aiming to determine whether intraosseous propofol could serve as a safe and effective alternative under circumstances where conventional inhalational techniques are contraindicated or not feasible.

MATERIALS AND METHODS

Twelve healthy male New Zealand White rabbits, aged 12 months and weighing 2.5 ± 0.2 kg, were obtained from an accredited laboratory animal facility. Animals were housed

individually in stainless-steel cages under controlled temperature (25–30 °C) and a 12 h light/12 h dark cycle, with ad libitum access to a commercial pelleted diet and water. Environmental enrichment was provided according to institutional welfare standards. All procedures were approved by the Institutional Animal Care and Use Committee (approval ID: IR.IAU.SHK.REC.1402.141) and complied with the ARRIVE guidelines. Rabbits were deemed eligible if they were clinically normal on physical examination, had hematological and biochemical values within the reference ranges, and showed no evidence of systemic disease. Animals with abnormal pre-anesthetic findings, poor body condition, or behavioral traits incompatible with safe handling were excluded from the study. Subjects were randomly allocated to two equal groups (n = 6) using a computer-generated simple randomization list prepared by a researcher who was not involved in the experiment. The sample size calculation considered a mean heart rate difference of 10 beats/min between groups, a standard deviation of 5 beats/min, $\alpha = 0.05$ (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, and the present experiment was conducted as a pilot study intended to provide preliminary data for future investigations involving a larger population size. Prior to anesthesia, all the rabbits were fasted for 2 h. Baseline jugular venous blood samples (5 ml) were aseptically collected for hematological and biochemical analyses.

In the first group, which received IO anesthesia with propofol, the proximal tibial metaphysis was clipped, prepared with povidone–iodine, and locally infiltrated with 0.5 mL of 1% lidocaine hydrochloride [Bayer Aflak, Lorestan, Iran], (Mazaheri-Khameneh *et al*., 2012; Kennedy *et al*., 2020). A 19-gauge needle was inserted into the medullary cavity at approximately 30° to the long axis. Correct placement was confirmed by marrow aspiration and free fluid infusion. The site was flushed with heparinised saline (10 IU/ml). Analgesic effectiveness was verified using hemostatic forceps for a pinch test applied to the inoculation area. No pain reflexes (withdrawal or vocalization) were observed, confirming the local desensitization. For anesthesia induction, propofol 1% [B. Braun, Melsungen AG, Germany] (12.5 mg/kg) was infused over 10 s via an automatic injection pump [SP-500; JMS Co., Ltd., Japan], followed by continuous infusion at 1 mg/kg/min for 30 min for maintenance of anesthesia.

In the second group, rabbits received 2 min of pre-oxygenation before gradual mask induction with isoflurane [Terrell, Pennsylvania, USA] in oxygen. Following the loss of gag and righting reflexes, orotracheal intubation was performed, and anesthesia was maintained with isoflurane in oxygen for 30 min using an anesthesia machine [SA-2; Dräger, Lübeck, Germany]. Isoflurane anesthesia was administered with supplemental oxygen, reflecting the conventional clinical setting, whereas the intraosseous propofol group was maintained under spontaneous ventilation without supplemental oxygen to simulate field conditions. This design aimed to evaluate propofol IO as an alternative anesthetic technique when oxygen or gas anesthesia systems are unavailable.

In both groups, heart rate, respiratory rate, rectal temperature, and oxygen saturation were measured before and immediately after induction and at 5 min intervals during anesthesia. Heart rate and respiratory rate were assessed using a stethoscope [Cardiology IV; Littmann, USA], rectal temperature with a digital thermometer [TK250; Accumed, Switzerland], and oxygen saturation with a multiparameter veterinary monitor [PM-7000VET; Zoncare, China]. At the end of anesthesia, the anesthetic agent was discontinued, and the animals were monitored until recovery. Jugular venous blood samples were collected for post-anesthetic hematological and biochemical analyses, targeting red blood cells, white blood cells, hemoglobin, hematocrit, glucose, cholesterol, creatinine, total protein, and liver enzymes (alkaline phosphatase, aspartate transaminase, alanine transaminase, and gamma-glutamyl transferase). Hematology analyses were performed using an automated cell counter [M-20; Medonic, Sweden], and biochemical analyses were performed using an automated analyzer [BS-200; Mindray, China].

Normality was assessed using the Kolmogorov–Smirnov test. Changes in HR and RR over time within and between groups were analyzed using repeated-measures ANOVA with Bonferroni-adjusted pairwise comparisons. Hematological data were compared using paired and independent t-tests, where appropriate. Statistical significance was set at $P < 0.05$. Statistical analyses were conducted using the SPSS software [version 12; SPSS Inc., Chicago, IL, USA].

RESULTS AND DISCUSSION

As shown in Table 1, intraosseous propofol administration (Group 1) resulted in significantly higher heart rates at 5 and 10 min after induction than isoflurane anesthesia (Group 2) ($P < 0.05$). The respiratory rate was consistently greater in Group 1 across most time points, whereas Group 2 exhibited more stable values throughout anesthesia ($P < 0.05$). Rectal temperature declined in both groups, but the decrease was more pronounced in Group 1, with significant intergroup differences at all recorded times, except at 10 min post-induction ($P < 0.05$). Oxygen saturation remained consistently higher in Group 2 during the anesthetic period ($P < 0.05$). Hematological evaluation (Table 2) showed post anesthetic reductions in hematocrit and hemoglobin, which were more evident in Group 2 ($P < 0.05$), whereas changes in Group 1 were minimal. Red blood cell counts decreased significantly in both groups, with lower overall values in Group 1 ($P < 0.05$). White blood cell counts declined slightly but without statistical significance ($P > 0.05$). Serum total protein remained

stable in Group 1 but increased significantly in Group 2, whereas serum creatinine concentrations increased in both groups, particularly in Group 2 ($P < 0.05$). Cholesterol levels decreased insignificantly in Group 1 ($P > 0.05$) but increased in Group 2 ($P < 0.05$). Liver enzyme activities decreased significantly in both groups following anesthesia ($P < 0.05$), with greater reductions in Group 1.

Table 1.
Cardiopulmonary and thermal parameters (mean ± SD) in rabbits anesthetized with intraosseous propofol (Group 1) or isoflurane (Group 2) before and at different time points after induction.

	HR (beats/min)		RR (breaths/min)		RT (°C)		SpO_2 (%)	
Time point (min)	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Pre-induction	224.0 ± 5.21	222.5 ± 5.96	59.2 ± 2.14	59.7 ± 1.63	38.50 ± 0.44*	38.82 ± 0.25	-	-
Post-induction	221.0 ± 5.09	224.2 ± 4.08	55.8 ± 3.37*	45.5 ± 6.38	37.18 ± 0.87*	38.00 ± 0.33	95.67 ± 1.51*	96.00 ± 1.26
5	221.2 ± 5.31*	228.3 ± 4.33	54.0 ± 3.03*	60.7 ± 1.86	35.82 ± 3.14*	37.38 ± 0.45	87.17 ± 2.71*	94.33 ± 0.82
10	218.2 ± 4.71*	222.2 ± 4.21	53.3 ± 2.73*	59.2 ± 1.17	35.80 ± 1.05	38.52 ± 1.25	85.17 ± 2.22*	94.17 ± 0.75
15	217.5 ± 3.99	223.7 ± 8.12	53.7 ± 3.39*	60.0 ± 1.26	32.17 ± 5.85*	36.75 ± 0.35	82.17 ± 2.14*	94.17 ± 0.75
20	218.2 ± 3.54	223.3 ± 3.78	54.0 ± 2.90*	60.8 ± 1.72	33.37 ± 4.47*	36.62 ± 0.48	82.83 ± 1.33*	93.67 ± 1.03
25	217.8 ± 2.93*	223.3 ± 3.78	54.3 ± 2.34*	61.2 ± 0.75	33.57 ± 4.63*	36.57 ± 0.58	84.33 ± 2.50*	93.50 ± 1.05
30	215.3 ± 1.75	217.3 ± 3.56	53.8 ± 2.32*	62.3 ± 1.21	33.60 ± 4.67*	36.27 ± 0.67	84.17 ± 1.94*	94.50 ± 1.22

HR, heart rate; RR, respiratory rate; RT, rectal temperature; SpO_2, blood oxygen saturation.
* Indicates a significant difference between Groups 1 and 2 at the same time point ($P < 0.05$).

Table 2.
Hematological and serum biochemical parameters (mean ± SD) in rabbits anesthetized with intraosseous propofol (Group 1) or isoflurane (Group 2) before and after induction.

	Group 1		Group 2	
Parameter	Pre-induction	Post-induction	Pre-induction	Post-induction
Hct (%)	44.50 ± 1.05	44.50 ± 1.38	44.83 ± 1.47	34.33 ± 0.82*
Hb (g/dl)	14.20 ± 1.10	13.82 ± 1.05	14.28 ± 0.86	11.73 ± 0.39*
RBC ($\times 10^6$/µL)	9.15 ± 0.14	4.68 ± 0.28*	9.05 ± 0.12	8.88 ± 0.07*
WBC ($\times 10^3$/µL)	5.30 ± 0.63	5.19 ± 0.61	5.54 ± 0.69	4.86 ± 0.56
TP (mg/dl)	5.97 ± 0.27	5.75 ± 0.30	5.95 ± 0.40	6.78 ± 0.28*
Glu (mg/dl)	85.98 ± 3.01	87.38 ± 2.88	85.82 ± 4.89	112.83 ± 10.09*
Cre (mg/dl)	1.48 ± 0.12	1.77 ± 0.01	1.49 ± 0.16	2.08 ± 0.07
ALT (U/L)	34.48 ± 1.26	31.97 ± 0.94*	30.30 ± 0.27	30.85 ± 0.39*
AST (U/L)	37.08 ± 0.63	33.41 ± 1.02*	37.05 ± 0.27	36.25 ± 0.40*
ALK (U/L)	37.78 ± 1.33	32.73 ± 1.32*	37.82 ± 0.93	37.60 ± 0.96*
GGT (U/L)	6.95 ± 0.72	5.03 ± 0.53*	7.20 ± 0.65	7.10 ± 0.65a

Hct, hematocrit; Hb, hemoglobin; RBC, red blood cells; WBC, white blood cells; TP, total protein; Glu, glucose; Cre, creatinine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALK, alkaline phosphatase; GGT, gamma-glutamyl transferase.
* Indicates a significant difference within groups (pre- vs. post-induction) or between groups at the same time point ($P < 0.05$).

Key findings indicated that intraosseous propofol produced significantly higher heart and respiratory rates during early anesthesia than isoflurane. This response is consistent with previous observations that injectable propofol may transiently preserve sympathetic tone and induce mild cardiovascular stimulation owing to its rapid central distribution and minimal baroreflex inhibition (Flecknell, 2015). In contrast, isoflurane anesthesia tends to cause peripheral vasodilation and mild respiratory depression effects that yield a more stable but lower heart rate and respiratory rate (Lamont & Grimm, 2024; Wenger, 2012). It should be noted that throughout anesthesia, no painful or surgical procedures were performed; the animals remained anesthetized for approximately 30 min without any manipulations capable of eliciting nociceptive reflexes. No behavioral or physiological signs indicative of pain were observed, confirming that variations in heart rate and respiratory rate reflected anesthetic-related physiological fluctuations rather than nociceptive responses.

These dynamics are consistent with the known lagomorph anesthetic physiology (Flecknell, 2015; Lamont & Grimm, 2024; Wenger, 2012). Rectal temperature declined progressively in both groups but was more marked with intraosseous propofol. Reduced heat generation during injectable anesthesia, limited evaporative loss control, and the absence of continuous oxygen flow likely contributed to a greater thermal drop (Flecknell, 2015). Isoflurane delivery with supplemental oxygen promotes steadier ventilation and thermoregulation, helping maintain higher peripheral perfusion and minimizing conductive heat loss. The higher oxygen saturation in Group 2 was directly attributable to the administration of oxygen via a precision vaporizer and mask, which supports alveolar oxygen exchange and prevents diffusion hypoxia (Brodbelt, 2009). Although rabbits in Group 1 did not receive supplemental oxygen, the saturation values remained within clinically acceptable limits, demonstrating adequate pulmonary ventilation when propofol was administered cautiously through the intraosseous route. The absence of oxygen supplementation in the intraosseous propofol group was intentional and designed to simulate conditions in which anesthesia must be performed in the field or under equipment-limited circumstances. Oxygen delivery was prepared and readily available for emergency use, but not administered, in order to evaluate the feasibility of intraosseous propofol as an alternative when inhalational anesthesia systems are not feasible.

The observed hematological and biochemical variations paralleled the mechanisms described in other studies. Decreases in hematocrit and hemoglobin, which are most evident with isoflurane, reflect anesthetic-induced splenic sequestration and vascular pooling (McKayla *et al*., 2025). The lack of a significant decline in white blood cells indicates a minimal acute inflammatory or stress-related hematological response over the short anesthetic interval (Flecknell, 2015, Miller, 2015). Slight increases in creatinine levels in both groups likely resulted from transient renal hypoperfusion but remained within normal physiological ranges, suggesting no overt renal compromise. Reduced hepatic enzyme activity and mild changes in total protein and cholesterol levels may reflect hemodilution and altered hepatic blood flow rather than hepatocellular injury. From a pathophysiological perspective, these findings reinforce the notion that the intraosseous route provides rapid and effective drug delivery to the central circulation, maintaining adequate hemodynamic balance without producing the pronounced vasodilation typical of inhalational anesthetics (Lamont & Grimm, 2024; Miller, 2015). Nevertheless, the less predictable control of depth and the absence of oxygen supplementation necessitate vigilant monitoring of cardiopulmonary and thermal parameters, particularly during long or critical procedures. The relatively small number of animals (n = 6 per group) limits the statistical power and generalizability of the results of this study. However, this study was intentionally designed as a pilot trial to generate preliminary data while complying with ethical requirements to minimize animal use. The relatively short anesthesia period represents another methodological constraint, but was chosen deliberately to evaluate early anesthetic stability, consistent with standard assessment periods in rabbits under experimental anesthesia. Post anesthetic recovery parameters, including induction time, anesthesia time, recovery time, and qualitative recovery scoring, were recorded and analyzed in the same experiment. Finally, post anesthetic gas analyses and blood pressure measurements were not performed, which should be addressed in future studies. Despite these limitations, our study provides novel comparative insights between the intraosseous propofol and inhalational isoflurane protocols. Under the conditions of the present study, intraosseous propofol demonstrated practical feasibility and acceptable physiological stability as an alternative to inhalational isoflurane in rabbits, especially in resource-limited or field situations where volatile agents are unavailable. However, maintains clear advantages in terms of oxygenation and thermoregulation. The intraosseous route has been demonstrated to be a safe and practical alternative for vascular access in rabbits and other species when venous catheterization is challenging. Several studies have confirmed that intraosseous administration does not cause significant discomfort, osteomyelitis, or long-term tissue injury when performed under aseptic conditions and with prior local desensitization. Moreover, behavioral and functional assessments after anesthesia revealed normal post-procedural recovery, supporting the overall safety of the procedure. These findings collectively confirm that short-term intraosseous infusion of propofol and other anesthetics is well tolerated and ethically acceptable in animals when performed with appropriate local anesthesia and monitoring (Daneshi, 2007; Marjani & Mehrvar, 2012; Mazaheri-Khameneh *et al*., 2012). Future investigations using larger cohorts, extended monitoring,

and correlations with detailed recovery metrics are warranted to refine anesthetic protocols and improve perioperative safety in small mammals.

Conflict of interest

Authors declare no conflict of interests

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