

Evaluation of clinical and paraclinical effects of intraosseous vs intravenous administration of propofol on general anesthesia in rabbits

Ramin Mazaheri-Khameneh, Farshid Sarrafzadeh-Rezaei*, Siamak Asri-Rezaei, Bahram Dalir-Naghadeh

Department of Clinical Sciences, Faculty of Veterinary Medicine, Urmia University, Urmia, Iran.

Article Info	Abstract
Article history: Received: 2 November 2011 Accepted: 15 February 2012 Available online: 15 June 2012	<p>This prospective study aimed to compare the intraosseous (IO) and intravenous (IV) effects of propofol on selected blood parameters and physiological variables during general anesthesia in rabbits. Thirty New Zealand White rabbits were studied. Six rabbits received IV propofol (group 1) and another 6 rabbits, were injected propofol intraosseously (Group 2) for 30 minutes (experimental groups). Rabbits of the third and fourth groups received IV and IO normal saline at the same volume given to the experimental groups, respectively. In the fifth group IO cannulation was performed but neither propofol nor normal saline were administered. Blood profiles were assayed before induction and after recovery of anesthesia. Heart and respiratory rates, rectal temperature, saturation of peripheral oxygen and mean arterial blood pressure were recorded. Heart rate increased significantly 1 to 5 minutes after induction of anesthesia in experimental groups ($P < 0.05$). Although mean arterial blood pressure decreased significantly from baseline, values remained above 60 mm Hg ($P < 0.05$). Respiratory rate decreased significantly in experimental groups, but remained higher in group 2 ($P < 0.05$). The lymphocyte count decreased significantly in group 1 ($P < 0.05$). The concentration of alkaline phosphatase in all rabbits, aspartate aminotransferase and gamma-glutamyl transferase in the first group and gamma-glutamyl transferase in the third group increased significantly ($P < 0.05$). Total bilirubin decreased significantly in group 2 ($P < 0.05$). All measured values remained within normal limits. Based on the least significant physiological, hematological and biochemical effects, the IO injection of propofol appears to be safe and suitable method of anesthesia in rabbits with limited vascular access.</p>
Key words: Propofol Blood profile Intraosseous injection Anesthesia Rabbit	

© 2012 Urmia University. All rights reserved.

بررسی اثرات کلینیکی و پاراکلینیکی تجویز داخل استخوانی پروپوفل در مقایسه با تزریق داخل وریدی برای ایجاد بیهوشی عمومی در خرگوش

چکیده

هدف از این مطالعه آینده نگر مقایسه اثرات داخل استخوانی و داخل وریدی پروپوفل بر شاخص های منتخب خون و متغیر های فیزیولوژیک طی بیهوشی عمومی در خرگوش می باشد. تعداد سی عدد خرگوش تحت مطالعه قرار گرفتند. شش خرگوش به صورت داخل وریدی (گروه ۱) و شش خرگوش دیگر به شکل داخل استخوانی (گروه ۲) پروپوفل را به مدت ۳۰ دقیقه دریافت کردند (گروه های آزمون). خرگوش های گروه ۳ و ۴ نرمال سالین با حجمی برابر با آنچه که در گروه های آزمون تزریق گردیده را به ترتیب دریافت نمودند. در گروه ۵ کانولاسیون داخل استخوانی اجرا شد ولی هیچ یک از داروهای پروپوفل یا نرمال سالین تزریق نگردید. پروفایل خونی خرگوش ها قبل القا و بعد از برگشت از بیهوشی تحت بررسی قرار گرفت. ضربان قلب، تعداد تنفس، دمای مقعدی، میزان اشباع اکسیژن خون محیطی و میانگین فشار خون شریانی ثبت گردیدند. ضربان قلب از دقیقه ۱ تا ۵ بعد از القا به طور معنی دار در گروه های آزمون افزایش یافت ($P < 0.05$). علیرغم کاهش معنی دار میانگین فشار خون شریانی نسبت به زمان پایه، این شاخص همواره بیشتر از ۶۰ میلیمتر جیوه باقی ماند ($P < 0.05$). تعداد تنفس در گروه های آزمون با کاهش معنی داری همراه بود، اما در گروه ۲ در حد بالاتری حفظ گردید ($P < 0.05$). شمارش لنفوسیت ها کاهش معنی داری در گروه ۱ نشان داد ($P < 0.05$). غلظت آلکالین فسفاتاز در همه خرگوش ها، آسپارات آمینوترانسفراز و گاما گلوتامیل ترانسفراز در گروه ۱ و گاما گلوتامیل ترانسفراز در گروه ۳ افزایش معنی داری داشت ($P < 0.05$). بیلی روبین تام در گروه ۲ دارای کاهش معنی داری بود ($P < 0.05$). تمامی شاخص های اندازه گیری شده در محدوده نرمال قرار داشتند. بر پایه تغییرات معنی دار مختصر فیزیولوژیک، هماتولوژیک و بیوشیمیایی، به نظر می آید که تزریق داخل استخوانی پروپوفل روشی مطمئن و مناسب برای ایجاد بیهوشی در خرگوش هایی با دسترسی عروقی محدود باشد.

واژه های کلیدی: پروپوفل، پروفایل خون، تزریق داخل استخوانی، بیهوشی، خرگوش

*Correspondence:

Farshid Sarrafzadeh-Rezaei, DVM, DVSc
Department of Clinical Sciences, Faculty of Veterinary Medicine, Urmia University, Urmia, Iran.
E-mail: f.sarrafzadeh@urmia.ac.ir

Introduction

Rabbits are the third most commonly anesthetized species, but have at least seven times more risks of anesthetic-related death compared to dogs and cats.¹ Currently, advanced diagnostic and surgical procedures requiring safe and adequate anesthesia are routinely performed on rabbits.² Tracheal intubation of rabbits and use of inhalation anesthetic can be quite complicated and time consuming.³ Intubation can cause trauma to the larynx, laryngospasm and tracheal lesions,⁴ so requires experience and technical dexterity. In small and laboratory animals, most anesthetics are administered intramuscularly because of the difficulty in obtaining intravenous (IV) access. The introduction of short acting hypnotic drugs like propofol prompted the development of alternative methods to inhalation anesthesia, i.e. total intravenous anesthesia (TIVA).⁵

Propofol, a non-barbiturate substituted isopropyl phenol is an IV anesthetic currently popular in human beings and animals as both a sole agent and as an adjunct in balanced anesthetic techniques.⁶ It has been used successfully to induce anesthesia in rabbits at doses of 5-15 mg kg⁻¹ of body weight.⁷⁻⁹ The major disadvantage of propofol is the need for IV administration. Other routes of administration such as the intraperitoneal or intramuscular route have no anesthetic effects at the doses investigated.⁸

The intraosseous (IO) route is effective for the administration of many drugs that induce chemical restraint.^{1-3,10} and the technique has almost completely replaced venous cut-down procedures in children, adults and animals.¹¹⁻¹³ When rapid venous catheterization is impossible the IO route has potential advantages in the induction and maintenance of general anesthesia with proper anesthetics. While considerable information on the pharmacokinetic, pharmacodynamic and hematological effects of propofol are available,^{8,14} its IO effects on hematological variables have not yet been studied.

The aim of this study was to compare the IO and IV effects of propofol on selected physiological and hematological variables during the induction and maintenance of anesthesia with propofol in rabbits.

Materials and methods

This study was approved by the ethics committee for Studies on Laboratory Animals of the Department of Clinical Sciences Review Board at the Faculty of Veterinary Medicine of Urmia University, Urmia, Iran. Thirty male New Zealand White rabbits, weighing 2.4 ± 0.5 kg, were examined before study and found to be in good health. They were kept in a controlled environment with a temperature of 20 ± 2 °C and had free access to commercial pellet diet (Niro-Sahand Co., Tabriz, Iran) and water until 1 hour before induction of anesthesia. Rabbits

were divided into two experimental and three control groups, each containing six. In all of the rabbits the skin of the dorsal base of one ear was infiltrated with 0.5-1 mL of lidocaine hydrochloride 1% solution (Kela Laboratoria, Hoogstraten, Belgium) to induce vasodilatation of the ear vessels to facilitate arterial and venous cannulation. Ten minutes later the central auricular artery and a marginal ear vein were cannulated with a 22 gauge over-the-needle catheter (Mediplus India Ltd., Haryana, India) for monitoring blood pressure, blood sampling and IV drug administration. The rabbits were restrained manually during IV and IO cannulation. The latter was accomplished by aseptically preparing the cranio-medial aspect of the tibia plateau before desensitizing the skin and periosteum with 0.5 mL of lidocaine hydrochloride 1% solution. A 22 gauge, 3 cm long bone marrow aspiration needle was inserted into the medullary cavity and the stylet removed before the needle was flushed with heparinized saline (10 IU mL⁻¹) solution and the needle secured in place. Rabbits were allowed to rest for 15 minutes after venous and arterial catheterization or osseous cannulation before pre-anesthetic data were collected.

The respiratory rate (RR) was determined by direct observation and heart rate (HR), saturation of peripheral oxygen (SpO₂) and rectal temperature were measured before induction of anesthesia, during the first 5 minutes and then at five-minute intervals throughout the anesthetic period directly by patient Monitor (General Meditech Inc, Shenzhen, China). The catheter of central auricular artery was connected to physiological pressure transducer (AD Instruments, Chalgrove, UK), data acquisition system (AD Instrument, Sydney, Australia) to enable monitoring of the direct mean arterial pressure (MAP) which was calculated as $MAP = diastolic\ BP + 0.3 (systolic\ BP - diastolic\ BP)$.⁸ All rabbits breathed room air spontaneously during the study.

In group 1, propofol 1% (12.5 mg kg⁻¹, B. Braun, Melsungen AG, Germany) was administered IV over 10 seconds for induction of anesthesia. Anesthesia was then maintained for 30 minutes by a constant rate IV propofol infusion (1 mg kg⁻¹ min⁻¹)⁹ using an automated delivery system (B. Braun Schiwa GmbH & Co. KG, Glandorf, Germany). In group 2, the dose and procedure for propofol administration was as for group 1 except that the IO route was used. The third group of animals was prepared as for group 1 but normal saline, was given. In group 4 normal saline was administered IO in the same way as propofol was administered in group 2. In group 5 only IO tibial cannulation was performed without administration of neither propofol nor normal saline.

Induction time was defined as the interval from administration of propofol to loss of righting reflex. Propofol anesthesia was discontinued after 30-minutes and recovery time was recorded. Anesthesia time was defined as the interval from loss of the righting reflex to its

return. Quality of anesthesia was evaluated according to the following anesthesia scale: 0= Severe reaction with violent movement; 1= Moderate reaction, able to stay in sternal position and mildly responsive to external stimuli (such as sound and hand waving); 2= Unable to stay in sternal recumbency and tending to stay in lateral recumbency. Hardly response to pinna and pedal withdrawal reflexes; 3= Deep general anesthesia, no reaction. All of reflexes were absent except corneal reflexes with mild reaction to stimuli. Recovery time was defined as a period between the end of propofol administration and returning of the righting reflex. Quality of recovery from induction to return of the righting reflex was evaluated by use of the following scale: 0 = Quite and smooth; 1 = Occasional thrashing and violent movement; 2 = Constant thrashing and violent movement; 3 = No effect.

Blood hematology and plasma chemistry profiles were compared in rabbits before propofol administration and after recovery from anesthesia and among rabbits of different groups on each occasion. An arterial blood sample of 2 mL was drawn into glass vials containing 1.0 mg mL⁻¹ ethyldiamine tetracetic acid (EDTA) to determine the hematological component according to the method of Mitruka and Rawnsley.¹⁵ Packed cell volume (PCV), was measured by microhematocrit tubes. Hemoglobin (Hb) was determined by the cyanmethemoglobin method. Total red blood cell (RBC) and white blood cell (WBC) counts were determined using an improved Neubauer hemocytometer method.¹⁶ Blood smears were air-dried and stained using Giemsa-Romanowski stain. Two hundred leukocytes were counted for each smear and classified as neutrophils (heterophils), eosinophils, basophils, lymphocytes and monocytes. Another 2 mL blood sample was allowed to clot in glass vials without coagulant and centrifuged at 3000 *g* for 20 minutes at 4°C. The serum was removed, frozen (-20 °C) and analyzed to determine the biochemical components. The serum was analyzed using an automated analyzer (Technicon, RA1000, USA) for total protein (TP), glucose (Glu), urea, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), creatinine (Cre), total bilirubin (TB), cholesterol (Chol), triglycerides (TG), phosphorus (P) and calcium (Ca).

Statistical analyses were performed using SAS version 9.1 (SAS Institute, Inc., Cary, USA). Data were analyzed as repeated measures using mixed models. The included fixed effects were treatment (route of administration), repeated effect of time, and their interaction term. The random effect was animals nested within treatments. For each parameter five covariance structures CS, UN, SP (POW), SP (GAU), and SP (SPH) were evaluated. The appropriate correlation structure was determined by identifying the smallest Akaike's information criterion. SP (POW) and SP (GAU) structures provided the best model fit for the parameters. LSMEANS statement was used to

calculate the least-squares means and standard errors. When the effects were significant, pair-wise differences between the least-squares means were compared using the PDIFF-option and Tukey's adjustment *t*-test in the LSMEANS statement. For each model, the Shapiro-Wilks test and examination of histograms and residual plots were used to explore the assumption of normality and homogeneity of variation. When the assumption of normality and/or homogeneity of variance were rejected, the data were transformed using the natural logarithm or square root to obtain normality or homogeneity of variation of the residuals. The level of significance was set at $P < 0.05$. Data are presented as least-square means \pm standard error of means (SEM).

Results

Induction of and recovery from anesthesia were uneventful in all experimental groups. Animals in groups 4 and 5 tolerated bone marrow cannulation under local anesthesia. The data for induction, anesthetic, and recovery time are presented in table 1. Statistical analysis showed no significant difference between anesthetic times in these groups ($P > 0.05$). All rabbits had a smooth, excitement-free and quiet recovery (Table 1).

There were no significant differences ($P > 0.05$) between groups 1 and 2 in mean HR, MABP, SpO₂ and body temperature at any given time. Mean baseline HR were 227.00 \pm 4.27 bpm (beats per minute) for group 1 animals and 221.00 \pm 4.27 bpm for those in group 2. Elevated HR was significant only 1 to 5 minutes after induction of anesthesia in both groups (Fig. 1). A significant decrease in mean RR ($P < 0.05$) was noted from 1 to 30 minutes during propofol anesthesia in each group, but RR were significantly high in group 2 at 1, 3, 4, 5, 10, 15, 20, and 30-minutes after induction compared to that of rabbits anesthetized by the IV route ($P < 0.05$) (Fig. 2).

The MABP and mean SpO₂ values decreased significantly compared to baseline value ($P < 0.05$). The MABP remained above 60 mm of Hg and pale mucous membranes were not observed in rabbits anesthetized by IV or IO propofol. These changes were significant for 30 minutes after induction in both groups (Fig. 3).

Table 1. The quality of anesthesia and recovery, time of induction, duration of anesthesia and time of recovery in rabbits receiving propofol IV and IO. Data are presented as mean \pm SEM.

Parameters	Group 1 (IV)	Group 2 (IO)
Time to induction (sec)	9.00 \pm 0.81	8.00 \pm 0.45
Time of anesthesia (min)	37.00 \pm 0.96	38.00 \pm 0.73
Time to recovery (min)	7.75 \pm 0.98	9.00 \pm 0.85
Quality of anesthesia	2	2
Quality of recovery	0	0

No significant differences were detected between anesthetic times between groups ($P > 0.05$).

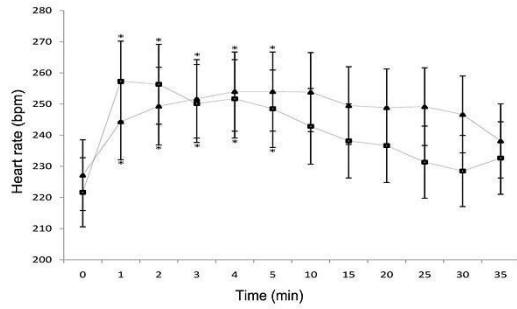


Fig. 1. Mean (\pm SEM) heart rate (bpm: beats per minute) of rabbits given propofol IV (Group 1 [triangles]) and IO (Group 2 [squares]) for induction and maintenance of anesthesia in experiment groups. * Significantly ($P < 0.05$) different from value at time 0.

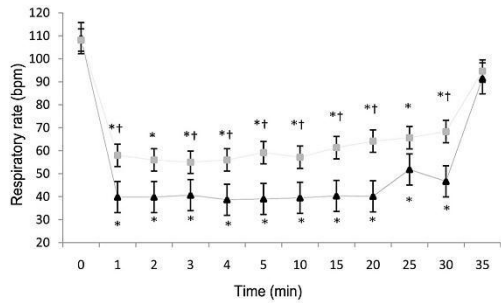


Fig. 2. Mean (\pm SEM) respiratory rate (bpm: breaths per minute) of rabbits given propofol IV (Group 1 [triangles]) and IO (Group 2 [squares]) for induction and maintenance of anesthesia in experiment groups. * Significantly ($P < 0.05$) different from value at time 0. † Significantly ($P < 0.05$) different between group 1 and group 2 groups.

The hematological and biochemical values obtained for rabbits before and after anesthesia in the experimental groups or any other interventions in the control groups are presented in Tables 2 and 3. Significant differences ($P < 0.05$) were found only in the concentration of lymphocytes in group 1 (Table 2). Packed cell volume values decreased in all groups, but this was not significant compared to the baseline values. There were also no significant decreases in Hb concentration, PCV and RBC. All hematological parameters were within the normal range after treatments in rabbits of the experimental and control groups. The WBC count increased after anesthesia although there were no significant differences between pre-and post-anesthetic

values. The blood plasma was characterized by a significant increase in ALP among all rabbits ($P < 0.05$). AST and GGT values were significantly increased in group 1 ($P < 0.05$). Increased GGT activity was noted in group 3 ($P < 0.05$). The total bilirubin concentration decreased significantly in group 2 only ($P < 0.05$). All biochemical parameters remained within normal limits (Table 3).

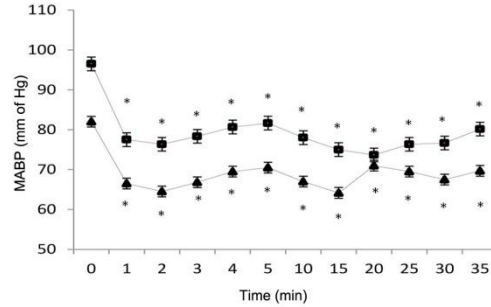


Fig. 3. Mean (\pm SEM) arterial blood pressure values of both experiment groups given propofol IV (Group 1 [triangles]) and IO (Group 2 [squares]) for induction (12.5 mg kg⁻¹) and maintenance (1 mg kg⁻¹ min⁻¹) of anesthesia. * Significantly ($P < 0.05$) different from value at time 0.

Discussion

Veterinary anesthesia demands increasingly safer techniques which could enable rapid recoveries and low incidence of adverse effects.^{17,18} In the present study the anesthetic and the pharmacodynamics effects of IO propofol was compared with that of its IV administration. This study demonstrated that the IO route was as effective as the IV route for propofol administration at doses inducing general anesthesia. The rate of absorption by the IO route was rapid and not different from IV injection, as revealed by the rapid induction. Similar findings have been described by other authors.^{2,3,10-12,19} Cardiovascular and respiratory effects of propofol administration in rabbits, dogs, rats, sheep and horse include heart rate elevation, post-induction apnea, hypoventilation, hypotension and decreased oxygen saturation.^{6,20-25} A significant tachycardia persisted for 5 minutes in the experimental groups (Fig. 1). The cause of increased HR during propofol anesthesia is not clear.²⁰ Since MABP decreased significantly in group 1

Table 2. Selected blood hematological parameters (SI Unit) in rabbits before and after drug administration. Values are presented as mean \pm SEM.

Groups	Time	Hb (mmol L ⁻¹)	PCV (L L ⁻¹)	RBC ($\times 10^{12}$ L ⁻¹)	WBC ($\times 10^9$ L ⁻¹)	Neutrophil ($\times 10^9$ L ⁻¹)	Eosinophil ($\times 10^9$ L ⁻¹)	Basophil ($\times 10^9$ L ⁻¹)	Monocyte ($\times 10^9$ L ⁻¹)	Lymphocyte ($\times 10^9$ L ⁻¹)
1	Before	8.26	0.39	5.90	8.70	3.56	0.05	0.17	0.20	4.67
	After	7.54	0.36	5.10	11.40	6.49	0.13	0.24	0.19	3.81*
2	Before	8.64	0.41	5.50	8.20	3.51	0.09	0.19	0.16	4.22
	After	8.34	0.40	4.80	10.50	5.90	0.17	0.21	0.21	3.97
3	Before	7.78	0.37	5.80	8.60	2.56	0.07	0.01	0.14	5.80
	After	7.26	0.35	5.60	8.80	2.92	0.08	0.00	0.26	5.50
4	Before	7.15	0.35	5.50	9.60	3.54	0.16	0.00	0.24	5.54
	After	6.82	0.34	5.40	9.90	4.20	0.24	0.00	0.28	5.21
5	Before	7.59	0.36	5.60	8.20	3.14	0.08	0.00	0.16	4.78
	After	7.40	0.35	5.60	7.50	2.84	0.10	0.00	0.17	4.37
SEM		0.23	0.01	0.28	0.63	0.02	0.00	0.00	0.00	0.01

* Significantly different from value at the time before drug administration ($P < 0.05$).

Table 3. Selected serum biochemical parameters (SI Unit) in rabbits before and after drug administration. Values are presented as mean \pm SEM.

Group	Time	TP (g L ⁻¹)	Glu (mmol L ⁻¹)	Urea (mmol L ⁻¹)	ALP (UL ⁻¹)	ALT (UL ⁻¹)	AST (UL ⁻¹)	GGT (UL ⁻¹)	Cre (μ mol L ⁻¹)	TB (μ mol L ⁻¹)	Chol (mmol L ⁻¹)	TG (mmol L ⁻¹)	Ca (mmol L ⁻¹)	P (mmol L ⁻¹)
1	Before	63.40	6.20	12.39	207.10	28.80	32.70	9.51	121.99	2.12	1.37	1.79	2.22	1.30
	After	59.00	6.10	12.01	222.17*	32.42	35.38*	11.81	108.73	1.96	1.45	1.74	2.46	1.25
2	Before	64.50	6.16	14.55	220.00	33.34	37.50	12.26	113.15	3.16	1.41	1.71	2.51	1.28
	After	61.50	6.21	16.40	239.44*	36.44	40.25	12.63	126.41	1.84*	1.38	1.86	2.71	1.50
3	Before	68.00	6.10	10.53	191.55	30.61	33.14	9.92	114.92	3.04	1.45	1.53	2.31	1.26
	After	69.50	6.63	11.73	201.80*	30.71	33.72	12.24	118.45	3.58	1.42	1.82	2.38	1.35
4	Before	67.00	6.41	10.79	211.20	32.55	34.90	11.00	106.96	2.61	1.50	1.60	2.48	1.39
	After	66.20	6.50	10.95	228.24*	32.73	36.80	12.55	102.54	2.90	1.45	1.64	2.49	1.45
5	Before	68.20	5.83	13.11	205.06	29.90	34.77	9.97	108.73	2.06	1.33	1.63	2.38	1.36
	After	65.10	6.42	13.29	216.22*	33.26	36.61	11.15	108.73	1.71	1.40	1.53	2.63	1.37
	SEM	2.20	0.18	0.75	7.74	1.36	1.33	0.53	5.21	0.22	0.08	0.08	0.08	0.07

* Significantly different from value at the time before drug administration ($P < 0.05$).

and 2 rabbits, the tachycardia was probably a reflex response to hypotension.²⁶ Generally, arterial vasodilatation and venodilatation, caused by reduction in sympathetic nervous outflow and a direct relaxant effect on vascular smooth muscle explains the lower blood pressures recorded during anesthesia.^{21,22,27-30}

Although significant decreases in SpO₂ values were recorded, cyanotic mucous membranes or ears were not observed; this may have been related to MABP values that persisted > 60 mmHg throughout anesthesia.⁸ In groups 1 and 2, the decrease in RR was significant from 1 to 30 minutes during anesthesia in both groups. However, the RR remained significantly higher in group 2 animals compared to those in group 1 (Fig. 2), a result which was also seen when thiopental, rather than propofol was used.³

The IV and IO administration of fluids also affect hematological profile.³¹ The foremost purpose of this study was to examine the effects of an IO administration of propofol on hematologic and biochemistry indexes in arterial blood samples. The 30-minute anesthesia of twelve rabbits using propofol IV or IO was safe. All hematological and biochemical parameters remained within the physiological range of healthy individuals.³²⁻³⁵

In sheep, all hematological parameters have been reported to be within the physiological limits during propofol anesthesia.³⁶ A decrease in PCV, Hb and RBC count values and an increase in WBC count values after surgery performed under acetylpromazine-propofol anesthesia in dogs have been reported.³⁷ It is known that propofol induces moderate systemic hypotension, arterial vasodilatation and venodilatation.⁴⁰ In the present study there were no significant differences in PCV, Hb, RBC and WBC values before and after administration of propofol in experimental groups. These values also remained unchanged in the control groups. The slight rise in the WBC concentration was evident in animals of the all groups of the current study. Prolonged periods of stress cause neutrophilia and lymphopaenia.⁴¹ In a study, marked changes in white blood cell distribution with a relative neutrophilia and lymphopenia were found in rabbits during air or lorry transport which was in direct relationship with cortisol levels of corresponding stress.⁴¹ The mild neutrophilia and lymphopenia in all groups of the current study with a marked lymphopenia observed in

group 1 rabbits could be explained as a reaction to the stress arising from manual handling and restraint and the cannulation of the auricular veins and arteries. The marked lymphopenia was only seen in group 1 rabbits, whereas this change was not significant in group 2. Eosinophil, basophil and monocyte counts were unaltered during the peri-anesthesia period, even in control groups.

Total protein, blood urea and serum creatinine values did not show any significant differences between treatment groups. As in other species, an elevated blood urea value in rabbits is associated with renal insufficiency. Low blood urea levels can also reflect hepatic dysfunction. Any changes in blood creatinine concentrations are due to changes in excretion and reflect renal function.⁴²

Hypercalcemia is seen in rabbits with chronic renal failure and impaired calcium excretion. Hyperphosphatemia can also result from impaired renal phosphorus excretion due to kidney disease. In the present study levels of total blood calcium or phosphorus after recovery of anesthesia in experimental or after described interventions in control groups remained unchanged and were within the normal range. These results may reflect the safety of IO or IV administration of propofol in relation to liver and kidney functions. In rabbits, hepatic ALT activity is lower than in other species and there is less organ specificity.⁴³ The ALT remained within the clinical normal range after recovery and after drug infusion in all groups. In rabbits, AST is found in the liver, heart, skeletal muscle, kidney and pancreas with the highest activity in the liver and skeletal muscle.⁴⁴ Physical exertion or tissue damage during blood collection can elevate results. Raised AST levels can be found in association with liver disease. Mild raised AST levels were seen after anesthesia in the experimental groups; however, it was significant only in group 1. A slight increase in AST values is reported in dogs when anesthetized with methotrimeprazine-propofol.⁴⁵

The liver is the predominant site for propofol glucuronidation in most species, although extra-hepatic glucuronidation in kidney and gastrointestinal tissues has been documented in several species.⁴⁶ Hepatic metabolism results in inactive, water-soluble sulfate and glucuronic acid metabolites that are excreted by the kidneys.^{14,47}

In rabbit GGT is located predominantly in the renal epithelium with low activity in the liver. Liver GGT is

present primarily in bile duct epithelial cells and is therefore an indicator of hepatobiliary disease rather than hepatocellular damage.⁴⁸ Atropine-medetomidine-propofol raises GGT activity levels in dogs.⁴⁹ In rabbits, ALP is present in nearly all tissues, in association with cell membranes, and especially in intestinal epithelium, renal tubules, osteoblasts, liver and placenta. In the present study a marked rise in ALP values was seen in animals of all groups ($P < 0.05$); the concentration of GGT was significantly higher in groups 1 and 3. Despite these, the values remained within the normal range. The unexpected ALP and GGT elevations could be explained in terms of the hepatic metabolism of propofol and the renal excretion of its metabolites by the kidneys. It is possible that the increased activity of ALP and AST resulted from restraint or various attempts at venous and arterial puncture. Abnormal cholesterol or triglyceride levels are most likely associated with dietary factors or hepatic dysfunction. The rabbit has low biliverdin reductase activity⁵⁰ and only 30% of biliverdin is converted to bilirubin. Bilirubin values can be affected by fasting. Atropine-medetomidine-propofol anesthesia raised blood triglycerides levels in dogs as well as increasing total bilirubin in dogs,⁴⁹ but these parameters remained unaffected during the current study. A significant decrease in the value of total bilirubin was seen in group 2. All blood biochemical parameters remained within the physiological limits in rabbits of this study under propofol anesthesia using either IV or IO route. Similar results were reported by Brzeski *et al.* in sheep with IV propofol anesthesia.³⁶ As no significant adverse effect was observed with IO injection of propofol on the physiological, hematological and biochemical parameters, the use of IO propofol could be recommended as a valuable and safe method of anesthesia in small animals with limited vascular access. However, caution should be taken on other aspects of IO anesthesia with propofol. For example, the effects of IO propofol on bone marrow are still unknown. In this regard, the clinico-pathologic and pathologic studies are underway (by authors) to determine whether there is any adverse effect.

Acknowledgments

This research was supported by the research fund of Urmia University, Urmia, Iran.

References

1. Brodbelt, D. Perioperative mortality in small animal anesthesia. *Vet J* 2009; 182(2):152-161.
2. Bennett RA, Schumacher J, Hedjazi-Haring K, et al. Cardiopulmonary and anesthetic effect of propofol administered intraosseously to green iguanas. *J Am Vet Med* 1998; 212:93-98.
3. Sarrafzadeh-Rezaei F, Dalir-Naghadeh B, Hassanpour H. Induction of general anesthesia with intraosseous injection of thiopental in rabbits. *Iran J Vet Res* 2008; 24:227-232.
4. Bateman L, Ludders JW, Gleed RD, et al. Comparison between facemask and laryngeal mask airway in rabbits during isoflurane anesthesia. *Vet Anesth Analg* 2005; 32(5): 280-288.
5. White PF. Intravenous (non-opioid) anesthesia. *Seminars in Anesthesia, Perioperative Medicine and Pain* 2005; 24:101-107.
6. Mama KR, Steffey EP, Pascoe PJ. Evaluation of Propofol as a General Anesthetic for Horses. *Vet Surg* 1995; 24:188-194.
7. Harcourt-Brown F. *Textbook of Rabbit Medicine*. 1st ed. Butterworth-Heinemann 2002; 85-86.
8. Lipman NS, Marini RP, Flecknell PA. Anesthesia and Analgesia in Rabbits. In: Fish RE, Brown MJ, Danneman PJ. Eds. *Anesthesia and analgesia in laboratory animals*. 2nd ed. San Diego: Academic Press 2008; 299-333.
9. Baumgartner CM, Koenighaus H, Ebner JK, et al. Cardiovascular effects of dipyrone and propofol on hemodynamic function in rabbits. *Am J Vet Res* 2009; 70:1407-1415.
10. Fonda D. Intraosseous anesthesia with propofol in red-eared sliders (*Trachemys scripta elegans*). *J Vet Anesth* 1999; 26:46-47.
11. Selby IR, James MR. The intraosseous route for induction of anesthesia. *Anesthesia* 1993; 48:982-984.
12. Leidel BA, Kirchhoff C, Bogner V, et al. Is the intraosseous access route fast and efficacious compared to conventional central venous catheterization in adult patients under resuscitation in the emergency department? A prospective observational pilot study. *Patient Saf Surg* 2009; 3:24.
13. Haas NA. Clinical review: Vascular access for fluid infusion in children. *Crit Care* 2004; 8:478-484.
14. Meyer RE, Fish RE. Pharmacology of injectable anesthetics, sedatives, and tranquilizers. In: Fish RE, Brown MJ, Danneman RJ, et al. *Anesthesia and analgesia in laboratory animals*. 2nd ed. San Diego: Academic Press 2008; 38-42.
15. Mitruka BM, Rawsley HM. Clinical, biochemical and hematological reference value in normal experimental animal. New York: Manson Publishing Inc. 1997; 35-50.
16. Brittain RT, D'arcy PF. Hematologic effects following the intravenous injection of propylene glycol in the rabbit. *Toxicol Appl Pharmacol*. 1962; 4:738-744.
17. Smith I, Terhoeve PA, et al. A multicenter comparison of the costs of anesthesia with sevoflurane or propofol. *Br J Anesth* 1999; 83(4):564-570.
18. Sarrafzadeh-Rezaei F, Asri-Rezaei S, Hadian M, et al. Thiopental sodium anesthesia following premedication of rabbits with vitamin C. *Veterinary Research Forum* 2010;1:7-11.
19. Valverde A, Bienzle D, Smith D, et al. Intraosseous

- cannulation and drug administration for induction of anesthesia in chickens. *Vet Surg* 1993; 22:240-244.
20. Lin Hui-Chu, Purohit RC, Powe TA. Anesthesia in sheep with propofol or with xylazine-ketamine followed by halothane. *Vet Surg* 1997; 26:247-252.
 21. Aeschbacher G, Webb AI. Propofol in rabbits. Long-term anesthesia. *Lab Anim Sci* 1993; 43:328-335.
 22. Aeschbacher G, Webb AI. Propofol in rabbits. Determination of an induction dose. *Lab Anim Sci* 1993; 43:324-327.
 23. Fujii Y, Hoshi T, Takahashi S, et al. Propofol decreases diaphragmatic contractility in dogs. *Anesth Analg* 1999; 89:1557-1560.
 24. Brammer A, West CD, Allen SL. A comparison of propofol with other injectable anesthetics in a rat model for measuring cardiovascular parameters. *Lab Anim* 1993; 27:250-257.
 25. Hughes JM, Nolan AM. Total intravenous anesthesia in greyhounds: pharmacokinetics of propofol and fentanyl; A preliminary study. *Vet Surg* 1999; 28:513-524.
 26. Peeters ME, Gil D, Teske E, et al. Four methods for general anesthesia in the rabbit: a comparative study. *Lab Anim* 1988; 22:355-360.
 27. Demeure dit Latte D, Bernard JM, Blanloeil Y, et al. Induction of anesthesia by propofol and hepatic blood flow in the rabbit. *Clin Physiol* 1995; 15:515-522.
 28. Glowaski MM, Wetmore LA. Propofol: Application in veterinary sedation and anesthesia. *Clin Tech Small Anim Pract* 1999; 1:1-9.
 29. MacLean RA, Harms CA, Braun-McNeill J. Propofol anesthesia in loggerhead (caretta caretta) sea turtles. *J Wildl Dis* 2008; 44:143-150.
 30. Pereira GG, Larsson MH, Yamaki FL, et al. Effects of propofol on the electrocardiogram and systolic blood pressure of healthy cats pre-medicated with acepromazine. *Vet Anesth Analg* 2004; 31:235-238.
 31. Ros SP, McMannis SI, Kowal-Vern A, et al. Effect of intraosseous saline infusion on hematological parameters. *Ann Emergency Med*, 1991; 20:243-245.
 32. Gillett CS. Selected drug dosages and clinical reference data. In: Manning PJ, Ringler DH, Newcomer CE. Eds. *The Biology of the Laboratory Rabbit*. 2nd ed. San Diego: Academic Press 1994; 467-472.
 33. Sanderson JH, Philips CE. Rabbits. In: *An Atlas of Laboratory Animal Hematology*. New York: Oxford University Press 1981; 6.
 34. Loeb WE, Quimby EW. Appendices. In: Loeb WE, Quimby EW. Eds. *The Clinical Chemistry of Laboratory Animals*. New York: Pergamon 1989; 419-509.
 35. Fox RR. The rabbit. In: Loeb WE, Quimby EW. *The Clinical Chemistry of Laboratory Animals*. New York: Pergamon 1989; 41-46.
 36. Brzeski W, Depta A, Jalyński M, et al. General anesthesia in sheep with the use of diprivan-propofol. *Medycyna Weterynaryjna* 1994; 50:215-217.
 37. Gill JR, Rodriguez JF, Ezquerro LJ, et al. Development of anesthesia and changes in the blood parameters in dogs medicated with propofol. *Medicina Veterinaria* 1996; 13:242-246.
 38. Kelawala NH, Parsania RR, Patil DB. Hematological and biochemical studies on ketamine, propofol and propofol-ketamine as general anesthesia in diazepam premedicated goats (*Capra hircus*). *Indian J Vet Surg* 1991; 12:17-20.
 39. Robertson SA, Johnston S, Beemsterboer J. Cardio-pulmonary, anesthetic and postanesthetic effects of intravenous infusions of propofol in Greyhounds and non-Greyhounds. *Am J Vet Res* 1992; 53:1027-1032.
 40. Branson KR, Gross ME. Propofol in veterinary medicine. *J Am Vet Med A* 1994; 204:1888-1890.
 41. Toth LA, January B. Physiological stabilization of rabbits after shipping. *Lab Anim Sci*, 1990; 40:384-387.
 42. Rosenthal K. Interpretation of selected clinical pathology values in ferrets and rabbits. In *Proceedings: The Atlantic Coast Veterinary Conference*, Atlantic City, USA 1997; 1-3.
 43. Harcourt-Brown F. *Textbook of Rabbit Medicine*. 1st ed. Oxford: Butterworth-Heinemann 2002; 140-164.
 44. Benson KG, Paul-Murphy J. Clinical pathology of the domestic rabbit. *Vet Clin N Am: Exotic Anim Pract* 1999; 2:539-552.
 45. Aguiar AJA, Hussni CA, Luna SPL, et al. Propofol compared with propofol/guaiphenesin after detomidine premedication for equine surgery. *J Vet Anesth* 1993; 20:26-28.
 46. Le Guellec C, Lacarelle B, Villard PH, et al. Glucuronidation of propofol in microsomal fractions from various tissues and species including humans: effect of different drugs. *Anesth Analg* 1995; 81:855-861.
 47. White PF, Romero G. Non-opioid intravenous anesthesia. In: Barash PG, Cullen BF, Stoelting RK. Eds. *Clinical Anesthesia*, 5th ed. Philadelphia: Lippincott Williams & Wilkins 2006; 334-353.
 48. McLaughlin RM, Fish RE. Clinical biochemistry and haematology. In: Manning PJ, Ringler DH, Newcomer CE. *The Biology of the Laboratory Rabbit*, 2nd ed. San Diego: Academic Press, 1994; 111-124.
 49. Komar E, Lipp J. Propofol anesthesia in dogs. In *Proceedings: The 5th International Congress of Veterinary Anesthesia*, Guelph, Canada. 1994; 205.
 50. Fekete S. Recent findings and future perspectives of digestive physiology in rabbits: a review. *Acta Vet Hungar* 1989; 37:265-279.