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Ketamine/xylazine anesthesia is safe in hemorheological point of view: a preliminary report

Ketamin/ksilazin anestezi hemoreolojik bakış açısından güvenlidir: bir ilk rapor

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Abstract

Purpose: Some anesthetic drugs are known to have influence on circulation due to hemorheological effects. We aimed to investigate the possible effects of ketamin-xylazine anesthesia, which is extensively used in experimental animal laboratories on hemorheological parameters.

Materials and methods: Adult, male Wistar-Albino rats were divided into two as control (pre-anesthesia) and post-anesthesia (n=17). Ketamin-HCl/Xylazine-HCl (90 mg/kg-10 mg/kg) were injected intraperitoneally. Intracardiac heparinized blood was collected either without anesthesia (control group) or after anesthesia (post-anesthesia group) following the loss of reflexes such as righting, cornea and withdrawal. Erythrocyte deformability was determined by an ektacytometer, while WBV (at shear rates of 38, 76 and 190 s-1) and PV (at 190 s-1 shear rate) at standard (40%) and otolog hematocrit (Hct) were measured via a cone-plate rotational viscometer.

Results: Mean time taken for the disappearance of righting reflex was 4±3.6, corneal reflex 8±6.8 and for withdrawal reflex 10±6.7 min. 90 mg/kg Ketamin-10 mg/kg Xylazine administration did not affect RBC deformability, WBV and PV of the rats.

Conclusion: These results demonstrate that, use of Ketamin/Xylazine anesthesia may be recommended especially when dealing with hemorheological, cardiovascular and hematological parameters.

Key words: Ketamin/xylazine, anesthesia, erythocyte deformability, viscosity, rat.

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Öz

Amaç: Bazı anestezik ilaçların hemoreolojik etkileri nedeniyle dolaşımı etkilediği bilinmektedir. Deney hayvan laboratuarlarında yaygın olarak kullanılan ketamin-ksilazin anestezisinin hemoreolojik parametreler üzerine olası etkilerini araştırmayı amaçladık.

Gereç ve yöntem: Yetişkin, erkek Wistar-Albino sıçanlar kontrol (anestezi öncesi) ve anestezi sonrası (n=17) olarak ikiye ayrıldı. Ketamin-HCl/Xylazine-HCl (90 mg/kg-10 mg/kg) intraperitoneal olarak enjekte edildi. İntrakardiyak heparinize kan anestezi olmadan (kontrol grubu) veya anestezi sonrası (anestezi sonrası grup) düzeltme, kornea ve geri çekme gibi reflekslerin kaybını takiben alındı. Eritrosit deformabilitesi bir ektasitometre ile belirlendi, WBV ise (38, 76 ve 190 s-1 kesme hızlarında) ve PV (190 sn-1 kesme hızında) standartta (%40) ve otolog hematokrit (Hct) bir koni plakalı rotasyonel viskometre ile ölçülmüştür.

Bulgular: Doğrultma refleksinin kaybolması için alınan ortalama süre 4±3,6, kornea refleksi 8±6,8 ve geri çekilme refleksi 10±6,7 dakika idi. 90 mg/kg Ketamin-10 mg/kg Xylazine uygulaması, sıçanların RBC deforme olabilirliğini, WBV ve PV'sini etkilememiştir.

Sonuç: Bu sonuçlar, Ketamin/Xylazine anestezisinin özellikle hemoreolojik, kardiyovasküler ve hematolojik parametrelerle uğraşırken önerilebileceğini göstermektedir.

Anahtar kelimeler: Ketamin/ksilazin, anestezi, eritrosit deformobilite, viskozite, sıçan.

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Introduction

Ketamine, which dissolves in water and oil reaches plasma peak concentration in 1-5 minutes (min) in intravenous (i.v.) application and in 15-30 min in oral administration [1, 2]. These differences may be due to incomplete absorption from the gastrointestinal tract and the first pass through the liver [3]. Ketamine is commonly used for sedation in short-term medical processes as endoscopy and circumcision during which striped muscle relaxation is unnecessary. It is also approved alone or in combination with other drugs for general anesthesia [4-7]. It binds to N-methyl-D-aspartate (NMDA) receptors in the posterior cornu of the medulla spinalis and provides long-term analgesic efficacy with a single application [8]. In humans, ketamine is used for short-term interventions such as circumcision and endoscopy for sedation.

Xylazine is a widely used transclysing agent for premedication. Sheep and goats are extremely sensitive to the influence of this substance [9]. A single bolus injection of the combination of ketamine and xylazine has advantages such as observation of the effect in a short time and duration. On the other hand; repeated doses and continuous infusion cause delays in recovery from anesthesia [10]. It has been reported that xylazine causes a decrease in heart rate and cardiac output, as well as a temporary hypertension and subsequent hypotension [9].

Main components of hemorheology are flow, erythrocyte deformability and aggregation [11] whereas hematocrit (Hct) and plasma viscosity (PV) are determinants of whole blood viscosity (WBV). Capillary diameter is smaller than that of the red blood cell (RBC) in many parts of the circulation. For this reason, erythrocytes need to change their shape in order to maintain tissue oxygenation [12]. Although some anesthetic drugs were demonstrated to cause microcirculatory disorders through cardiovascular and hemorheological effects [13-16], the influence of ketamine/xylazine anesthesia, on hemorheological parameters remains unknown. In order to minimize or eliminate side effects of ketamine such as high muscular tone, chills, increase in body temperature, increase in intraocular and arterial pressure, it is often used in combination with xylazine [17]. Ketamine/xylazine anesthesia is often used in laboratory animal studies [18]. If this combination affects hemodynamics of the animal like other anesthetics outlined above, having this knowledge would be important to discuss the results of especially cardiovascular, hemorheological studies. Therefore, we aimed to investigate the effects of ketamine/xylazine (90 mg/kg ketamine-HCl/10 mg/kg xylazine-HCl) anesthesia, on RBC deformability, WBV and PV in rats. Ketamine and Xylazine doses and way of delivery were selected based on the doses and application way frequently used for anesthesia during experimental studies.

Material and methods

Adult, male 250-300 g, 4-6 months old Wistar-Albino rats were used in experiments. Ketamine-HCl/Xylazine-HCl (90 mg/kg/10 mg/kg) were injected intraperitoneally. Rats were randomly grouped as control (pre-anesthesia, n=17) and post-anesthesia. Heparinized (15 IU/ml) blood was drawn either without anesthesia (control group) or following anesthesia after the loss of righting, corneal and withdrawal reflexes (post-anesthesia group). Equal amount of subcutan (s.c.) saline was injected after intracardiac blood collection to prevent rats from dehydration. Disappearing time of reflexes was determined as the period from injection of the anesthetic agent (ketamine/xylazine) to the loss of reflexes. The animal was placed on its back and failure to right itself was considered as the loss of righting reflex. The animal that rights itself was deemed as being awake. The corneal reflex was evaluated by gently pressing on the cornea with a piece of cotton. The paw withdrawal reflex was evaluated by pressing interdigital hind paw skin with hemostatic forceps in a manner that would not cause tissue damage [19].

Animals were provided by Pamukkale University Experimental Animals Research Unit (DEHAB). The animals were examined closely while under anesthesia and after the recovery from anesthesia. The study was approved by Animal Experiments Ethics Committee and conducted in accordance with the guidelines of this committee.

Erythrocyte deformability measurements

Erythrocyte deformability was measured using an ectacytometer (LORCA; RRMechatronics, Hoorn, The Netherlands) at various fluid shear stresses between 0.3 and 30 Pa [20]. All measurements were performed out at 37°C. A low hematocrit (Hct) erythrocyte suspension in an isotonic polyvinylpyrrolidone medium (4% polyvinylpyrrolidone 360 solution; MW 360kD; Sigma P 5288; St. Louis, MI) was sheared in a device involving a glass cup and a precisely fitting bob, with a gap of 0.3 mm. After the direction of a laser beam, the diffraction pattern produced by the deformed cells was analyzed. An elongation index (EI) was calculated as EI=(L-W)/(L+W), where L and W are the length and width of the diffraction pattern.

Determination of whole blood and plasma viscosities

WBV [at shear rates of 38, 76 and 190 s^{-1} at autologous and standard (40%) Hct] and PV (at 190 s^{-1} shear rate) were determined with a Wells-Brookfield cone-plate rotational viscometer (model DV-II+Pro; Brookfield Engineering Labs, Middleboro, MA) at 37°C. The Hct value was adjusted to 0.4 L/L by removing or adding a calculated amount of autologous plasma obtained after centrifugation at 1400×g, 6 min. Hct was measured by a Hct ruler.

Statistical analysis

All statistical analyses were performed using SPSS 25.0 software (IBM SPSS Statistics 25 software (Armonk, NY: IBM Corp.). Given that the difference between independent groups would have a large effect size (d=0.89), a power analysis was performed before the study. It was observed that when at least 34 rats were included (at least 17 rats per group), that would result in 80% power with a confidence level of 95%. Continuous data were reported as mean ± standard deviation (SD). For testing normality, Shapiro Wilk test was used. If parametric test conditions were satisfied Paired Samples t test; and if parametric test conditions were not satisfied Wilcoxon signed rank test was used for pairwise comparisons. $P<0.05$ was considered statistically significant.

Results

Disappearing time of reflexes after ketamine/xylazine (90 mg/kg-10 mg/kg) anesthesia are demonstrated in Table 1. RBC deformability (i.e., the elongation index, EI) was measured at 9 shear stresses between 0.3 and 30.0 pascal (Pa) and shown in Table 2. Ketamine/xylazine anesthesia applied in the current study, did not cause any statistically significant alteration in RBC deformability. Table 3 demonstrates that the anesthesia yielded no statistically significant change in WBVs determined at 3 shear rates between 38 and 190 s^{-1} and PV measured at 190 s^{-1}.

Table 1. Disappearing time of reflexes after ketamine/xylazine (90 mg/kg/10 mg/kg) anesthesia

Disappearing Time of Reflexes	After Anesthesia Mean ± Standard Deviation (min)
Righting Reflex	4.040±3.600
Corneal Reflex	8.020±6.800
Withdrawal Reflex	10.340±6.720

Table 2. RBC deformability measurements before and after ketamine/xylazine (90 mg/kg/10 mg/kg) anesthesia

EI (Pa)	Before Anesthesia Mean ± Standard Deviation	After Anesthesia Mean ± Standard Deviation	*p* value
0.30	0.101±0.025	0.113±0.020	0.149
0.53	0.161±0.031	0.167±0.026	0.486
0.95	0.251±0.032	0.251±0.031	0.942
1.69	0.347±0.026	0.335±0.0431	0.301
3.00	0.431±0.023	0.419±0.038	0.244
5.33	0.495±0.019	0.479±0.042	0.209
9.49	0.539±0.018	0.521±0.045	0.088
16.87	0.573±0.017	0.551±0.047	0.058
30.00	0.596±0.020	0.575±0.040	0.061

Table 3. Whole blood viscosity (WBV), plasma viscosity (PV) and hematocrit (Hct) measurements before and after ketamine/xylazine (90 mg/kg/10 mg/kg) anesthesia

	Before Anesthesia Mean ± Standard Deviation	After Anesthesia Mean ± Standard Deviation	*p* value
WBV at native Hct (38 s^{-1})	5.738±0.401	5.530±0.665	0.343
WBV at native Hct (76 s^{-1})	4.528±0.368	4.470±0.531	0.257
WBV at native Hct (190 s^{-1})	4.123±0.687	3.754±0.673	0.081
WBV at standard (%40) Hct (38 s^{-1})	6.010±0.506	5.510±0.682	0.800
WBV at standard (%40) Hct (76 s^{-1})	4.935±0.292	4.288±0.697	0.857
WBV at standard (%40) Hct (190 s^{-1})	4.317±0.530	3.714±0.710	0.537
PV (190 s^{-1})	1.925±0.254	1.808±0.233	0.589
Hct (%)	40.929±5.061	40.294±6.362	0.736

Discussion

Ketamine is widely used due to its analgesic and antiarrhythmic anesthetic effects. It shows its effect faster and quicker than other anesthetics [21]. Although ketamine has side effects such as bradycardia, conduction disorders, hypotension, respiratory depression and hypoxia, It is frequently used for its sedative, analgesic and musculorelaxane effects [21, 22]. Ketamine is known to interact with NMDA receptors, voltage sensitive calcium channel receptors, opioid, monoaminergic and muscarinic receptors. Unlike other injectable anesthetics ketamine stimulates alpha-2 adrenergic receptors without interacting with GABA receptors. Ketamine is one of the first anesthetics used in veterinary medicine for analgesic and sedative purposes [23, 24]. Xylazine hydrochloride is defined as the general name of 2- (2.6, dimethylphenylamino) -4H-5.6 dihydro-1.3 thiazin hydrochloride, which is a commonly used drug in veterinary practice due to its intensive sedative, analgesic and myorelaxane properties [25]. Its sedative and analgesic effect is caused by the stimulation of α2 adrenoreceptors in central nervous system (CNS). The muscle relaxant effect occurs by preventing intraneuronal transmission in CNS [26]. The cardiovascular system depression or arrhythmia observed following treatment with xylazine alone or in combination may limit its use [27]. Acquisition and interpretation of data, technical procedures When xylazine is administered as an i.v bolus injection, bradycardia and short-term (5-10 min) hypertension, followed by a decrease in cardiac output and blood pressure over a longer period of time occurs [28]. These effects are observed in almost all species [29]. Ketamine-HCl/Xylazine-HCl combination is commonly used for anesthetic purposes in experimental animal studies. Results of the current study

demonstrate for the first time that despite their cardiovascular side effects, i.p. administration of Ketamine-HCl/Xylazine-HCl (90 mg/kg-10 mg/kg) does not affect RBC deformability, WBV, PV and Hct values. Ketamine and Xylazine doses were selected based on the doses commonly used for anesthesia in our laboratory.

Disappearing time of reflexes was investigated in order to determine the beginning of the anesthesia period. Janssen et al. [30] injected 80 mg/kg ketamine and 10 mg/kg xylazin to rats and found that righting reflex was lost after 3±1.3 min. Giroux et al. [31] also injected the same dose of i.p. ketamine and xylazine to 3, 6, 12 and 18 months old rats. They noted that, both corneal and withdrawal reflexes were absent on the 15th min. When the same authors injected i.p. 125 mg/kg ketamine and 10 mg/kg xylazine to 3, 6, 12 months old rats, they once more observed disappearance time of corneal and withdrawal reflexes at the 15th min [19]. They concluded that, age of rats and the doses of anesthesia injected mostly affects the recovery time of the reflexes, but not the disappearance time. Our findings, partly similar to the results of the studies discussed above indicated the loss of righting reflex as 4±3.6 min, corneal reflex as 8±6.8 min, and withdrawal reflex as 10±6.7 min in response to i.p. administration of ketamine-HCl/xylazine-HCl (90 mg/kg-10 mg/kg) to 4-6 months old rats.

Effectual blood supply plays an important role in proper maintenance of tissue metabolism and thus, function. Blood supply and the metabolic tissues demand are kept in balance by vascular control mechanisms [32]. Much importance was not given to the hemorheological parameters as determinants of resistance to flow for many decades. On the other hand, vascular component has been studied extensively. Impaired hemorheological properties are known to affect tissue perfusion negatively [33, 34]. The high deformability of the RBC facilitates blood flow even at high hematocrit, particularly in the microcirculation [35].In addition, the ability of the entire RBC to deform is of crucial importance for performing its function in oxygen delivery. Deformability is also a determinant of the cell survival time in the circulation [11]. WBV is one of the components of the resistance to blood flow and perfusion of the microcirculation, although other factors such as pressure difference, sympathetic system activity, resistance of arterioles, local metabolic demand, local vasodilators such as nitric oxide and prostacyclin and other factors take place in the whole picture [36, 37]. The main determinants of WBV are PV, Hct, shear stress and shear rate, RBC deformability, RBC aggregation, fibrinogen concentration. and temperature [36]. This is why we measured WBV at otolog and standard Hct at different shear rates. Erythrocyte deformability is known as a major determinant at high shear stress whereas erythrocyte aggregation determines the WBV at low shear stress [38].

Some anesthetics are known to alter hemorheological parameters [16]. 40 mg/kg morphine injection caused decrement in erythrocyte deformability and increment in RBC membrane fluidity. In line with these results, it has been suggested that the secondary structure of erythrocyte membrane proteins changes and RBC membrane opioid receptors are directly affected. Morphine is an amphipathic substance and its hydrophobic part can penetrate the lipid barrier. A decrease in membrane lipid fluidity and an increase in osmotic fragility yields hemolysis easily [15]. The time-dependent effects of in vitro propofol on RBC aggregation, erythrocyte deformability and morphology at plasma concentrations required for sedation and general anesthesia were investigated in another study. Blood samples obtained from healthy individuals were incubated with propofol at plasma concentrations of 0, 2, 4 μg/ml for 1, 2 and 4 hours in a 37°C water bath. Similar to our results, propofol did not affect erythrocyte deformability, aggregation and morphology over a 4 hour incubation period, indicating that that propofol does not negatively affect microcirculation at normal clinical doses [39]. Mokken et al. [13] compared hemorheological parameters of patients who were anesthetized with fentanyl alone and propofol fentanyl combination. Postoperative hematocrit value was found to be decreased. A significant increase was found in all shear rates in WBV corrected for low hematocrit value in propofol + fentanyl group. No significant alteration in RBC deformability was observed. On the other hand, when WBV in chronic heroin users was evaluated, a significant reduction in WBV at all shear stresses and an increase in erythrocyte

aggregation was observed [40]. Combined halothane and pentobarbital administration was shown to cause decrement in erythrocyte deformability and antioxidant enzymes [14].

In conclusion, results of the current study demonstrate that Ketamine-HCl/Xylazine-HCl anesthesia at a dose of 90 mg/kg-10 mg/kg is safe in hemorheological point of view. This type of anesthesia may be preferred especially when dealing with hemorheological, cardiovascular and hematological parameters. On the other hand, current study may be accepted as a preliminary one. Studies investigating effects of Ketamine-HCl/Xylazine-HCl combination on hemorheological parameters in other species, with different doses and application ways may be conducted in order to clarify the subject.

Conflict of interest: No conflict of interest was declared by the authors.

References

1. Lauretti GR, Lima IC, Reis MP, Prado WA, Pereira NL. Oral ketamine and transdermal nitroglycerin as analgesic adjuvants to oral morphine therapy for cancer pain management. Anesthesiology 1999;90:1528-1533. https//doi.org/10.1097/00000542-199906000-00005
2. Azevedo VM, Lauretti GR, Pereira NL, Reis MP. Transdermal ketamine as an adjuvant for postoperative analgesia after abdominal gynecological surgery using lidocaine epidural blockade. Anesth Analg 2000;91:1479-1482. https//doi.org/10.1097/00000539-200012000-00034
3. Grant IS, Nimmo WS, Clements JA. Pharmacokinetics and analgesic effects of i.m. and oral ketamine. Br J Anaesth 1981;53:805-810. https//doi.org/10.1093/bja/53.8.805
4. Duman RS. The dazzling promise of ketamine. Cerebrum 2018;2018:04-18.
5. Anghelescu DL, Tesney JM. Neuropathic pain in pediatric oncology: a clinical decision algorithm. Paediatr Drugs 2019;21:59-70. https//doi.org/10.1007/s40272-018-00324-4
6. Chomchai S, Phuditshinnapatra J, Mekavuthikul P, Chomchai C. Effects of unconventional recreational drug use in pregnancy. Semin Fetal Neonatal Med 2019;24:142-148. https//doi.org/10.1016/j.siny.2019.01.010
7. Louer R, McKinney RC, Abu Sultaneh S, Lutfi R, Abulebda K. Safety and efficacy of a propofol and ketamine based procedural sedation protocol in children with cerebral palsy undergoing botulinum toxin a injections. PM R 2019;11:1320-1325. https//doi.org/10.1002/pmrj.12146
8. Malinovsky JM, Lepage JY, Cozian A, Mussini JM, Pinaudt M, Souron R. Is ketamine or its preservative responsible for neurotoxicity in the rabbit? Anesthesiology 1993;78:109-115. https//doi.org/10.1097/00000542-199301000-00016
9. Grant C, Upton RN. Cardiovascular and haemodynamic effects of intramuscular doses of xylazine in conscious sheep. Aust Vet J 2001;79:58-60. https//doi.org/10.1111/j.1751-0813.2001.tb10642.x
10. Lin HC, Purohit RC, Powe TA. Anesthesia in sheep with propofol or with xylazine-ketamine followed by halothane. Vet Surg 1997;26:247-252. https//doi.org/10.1111/j.1532-950x.1997.tb01494.x
11. Stuart J, Nash GB. Red cell deformability and haematological disorders. Blood Rev 1990;4:141-147. https//doi.org/10.1016/0268-960x(90)90041-p
12. Gyawali P, Richards RS, Bwititi PT, Nwose EU. Association of abnormal erythrocyte morphology with oxidative stress and inflammation in metabolic syndrome. Blood Cells Mol Dis 2015;54:360-363. https//doi.org/10.1016/j.bcmd.2015.01.005
13. Mokken FC, Henny CP, Gelb AW, et al. The effects of propofol compared to high-dose fentanyl anesthesia on rheologic parameters in coronary artery surgery. J Cardiothorac Vasc Anesth 1993;7:10-16. https//doi.org/10.1016/1053-0770(93)90111-w
14. Yesilkaya A, Ertug Z, Yegin A, Melikoglu M, Baskurt OK. Deformability and oxidant stress in red blood cells under the influence of halothane and isoflurane anesthesia. Gen Pharmacol 1998;31:33-36. https//doi.org/10.1016/s0306-3623(97)00426-6
15. Nie X, Wen ZY, Yan ZY, Huang L, Sun D, Cheng B. Effects of morphine on rheological properties of rat red blood cells, Clin Hemorheol Microcirc 2000;22:189-195.
16. Alet AI, Basso SS, Castellini HV, Delannoy M, Alet N, D'Arrigo M, Riquelme BD. Hemorheological in vitro action of propofol on erythrocytes from healthy donors and diabetic patients. Clin Hemorheol Microcirc 2016;64:157-165. https://doi.org/10.3233/ch-162054
17. Afshar SF, Baniadam A, Marashıpour PS. Effect of xylazine-ketamine on arterial blood pressure, arterial blood pH, blood gases, rectal temperature, heart and respiratory rates in goats, Bull Vet Inst Pulawy 2005;49:481-484.
18. Fish E, Brown MJ, anneman PJ. Anesthesia and Analgesia in Laboratory Animals, 2nd ed. In: San Diego: American College of Laboratory Animal Medicine Series: Academic Press, 2008.
19. Giroux MC, Hélie P, Burns P, Vachon P. Anesthetic and pathological changes following high doses of ketamine and xylazine in Sprague Dawley rats. Exp Anim 2015;64:253-260. https://doi.org/10.1538/expanim.14-0088

20. Hardeman MR, Goedhart PT. Methods in Hemorheology. In: Handbook of Hemorheology and Hemodynamics, Baskurt OK, Hardeman MR, Rampling MW, Meiselman HJ. (eds), IOS Press: Netherlands, 2007.
21. Haskins SC. Anaesthetic management of patients with cardiopulmonary disorders. In: World Veterinary Congress Proceedings, Tokyo,1995:195.
22. Rohrbach H, Korpivaara T, Schatzmann U, Spadavecchia C. Comparison of the effects of the alpha-2 agonists detomidine, romifidine and xylazine on nociceptive withdrawal reflex and temporal summation in horses. Vet Anaesth Analg 2009;36:384-395. https://doi.org/10.1111/j.1467-2995.2009.00466.x
23. Hall LW, Clarke KW. Veterinary anaesthesia. 9th ed. London: Baillière Tindall. 1991:25-29.
24. Paddleford RR, Harvey RC. Alpha 2 agonists and antagonists, Vet Clin North Am Small Anim Pract 1999;29:737-745. https://doi.org/10.1016/s0195-5616(99)50058-2
25. Clarke KW. and Hall LW. A survey of anaesthesia in small animal practice: AVA/BSAVA Report Vet Anaesth Analg 1990;17:4-10. https://doi.org/10.1111/j.1467-2995.1990.tb00380.x
26. Gokhan GA, Gurer IE, Akyuz M, Tuncer R. A case of extraventricular neurocytoma of the spinal cord, Neuropathology 2008;28:322-325. https://doi.org/10.1111/j.1440-1789.2007.00843.x
27. Cassu RN, Melchert A, Canoa JT, Martins PD. Sedative and clinical effects of the pharmacopuncture with xylazine in dogs. Acta Cir Bras 2014;29:47-52. https://doi.org/10.1590/S0102-86502014000100007
28. Sinclair MD. A review of the physiological effects of alpha2-agonists related to the clinical use of medetomidine in small animal practice. Can Vet J 2003;44:885-897.
29. Gaynor JS, Muir W. Handbook of Veterinary Pain Management. London, Mosby, 2000.
30. Janssen CF, Maiello P, Wright MJ, Kracinovsky KB, Newsome JT. Comparison of atipamezole with yohimbine for antagonism of xylazine in mice anesthetized with ketamine and xylazine. J Am Assoc Lab Anim Sci 2017;56:142-147.
31. Giroux MC, Santamaria R, Hélie P, Burns P, Beaudry F, Vachon P. Physiological, pharmacokinetic and liver metabolism comparisons between 3-, 6-, 12- and 18-month-old male Sprague Dawley rats under ketamine-xylazine anesthesia. Exp Anim 2016;65:63-75. https://doi.org/10.1538/expanim.15-0039
32. Akbudak IH, Kucukatay V, Kilic Erkek O, Ozdemir Y, Bor Kucukatay M. Investigation of the effects of major ozone autohemotherapy application on erythrocyte deformability and aggregation. Clin Hemorheol Microcirc 2019;71:365-372. https://doi.org/10.3233/CH-180417
33. Chien S. Biophysical behavior of red cells in suspensions in: the red blood cells. In: Surgenor DM (ed), 2.Academic Press, New York, 1975:1031-1133.
34. Baskurt OK, Meiselman HJ. Blood rheology and hemodynamics. Semin Thromb Hemost 2003;29:435-450. https://doi.org/10.1055/s-2003-44551
35. El Sayed MS. Effects of exercise and training on blood rheology. Sports Med 1998;26:281-292. https://doi.org/10.2165/00007256-199826050-00001
36. Bagher PI, Segal SS. Regulation of blood flow in the microcirculation: role of conducted vasodilation. Acta Physiol (Oxf) 2011;202:271-284. https://doi.org/10.1111/j.1748-1716.2010.02244.x
37. Hellsten Y, Nyberg M, Jensen LG, Mortensen SP. Vasodilator interactions in skeletal muscle blood flow regulation. J Physiol 2012;590:6297-6305. https://doi.org/10.1113/jphysiol.2012.240762
38. Herńandez GN, Dabin C, Gayol del MC, Rasia ML. Haemorheological variables in a rat model of hypertriglyceridaemic obesity and diabetes. Vet Res Commun 2002;26:625-635. https://doi.org/10.1023/a:1020920820767
39. Kim YH, Chung HG, Myung SA. In vitro effect of clinical propofol concentrations on red blood cell aggregation and deformability. Clin Hemorheol Microcirc 2012;51:287-292. https://doi.org/10.3233/CH-2012-1535
40. Antonova N, Zvetkova E, Ivanov I, Savov Y. Hemorheological changes and characteristic parameters derived from whole blood viscometry in chronic heroin addicts. Clin Hemorheol Microcirc 2008;39:53-61.

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Contributions of authors

I.H.A. conceptualized and designed the article, I.H.A., M.B.K., O.K.E. coordinated and collected the clinical data, reviewed the literature, wrote and drafted the initial manuscript. O.K.E., E.B.T., H.A. kept statistics, I.H.A., E.B.T., M.B.K. wrote text evaluation and discussion. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.