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# Hematological and biochemical parameters in Spotted Paca (*Cuniculus paca*) undergoing pharmacological restraint and general anesthesia

[*Parâmetros hematológicos e bioquímicos em Cuniculus paca sob contenção química e anesthesia geral*]

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## ABSTRACT

The aim of this study was to assess the effects of chemical restraint, general anesthesia and opioid treatment on hematological components in *Cuniculus paca*. Eight healthy, adult, captivity female animals , underwent three laparoscopic procedures with a 15-day interval were evaluated. After physical restraint, an association of ketamine (25mg/kg) and midazolam (0.5mg/kg) was administered intramuscularly for chemical restraint. Posteriorly, anesthesia was induced and maintained with isoflurane; and randomly administered methadone (0.5mg/kg), tramadol (5mg/kg) or saline-placebo (0,1mL/kg) intramuscularly. After pharmacological restraint and in the final laparoscopy stage, venous blood samples were obtained for complete blood count, total plasma protein (TP), creatinine, alanine aminotransferase (ALT), sodium, potassium, chloride and ionized calcium analysis. During general anesthesia, hemoglobin, TP concentration and lymphocytes decreased (P=0.029; <0.001; 0.022 respectively), whereas the potassium levels increased (P=0.034). In conclusion, chemical restraint with ketamine/midazolam association causes a slight decrease in blood cellular components. Isoflurane anesthesia for laparoscopic procedure lead to decrease in hemoglobin, lymphocytes and protein concentrations, while potassium increased, without any influence from the tramadol or methadone treatment. However, these alterations were transient, and its hematologic values can collaborate in carrying out epidemiological, pathophysiological or case studies in the *Cuniculus paca*.

Keywords: isoflurane, ketamine, methadone, midazolam, rodents

## RESUMO

*O objetivo do presente estudo foi avaliar os efeitos de contenção química, anestesia geral e tratamento com opiáceos nos parâmetros hematológicos em Cuniculus paca. Foram avaliados oito animais saudáveis, fêmeas, adultas, de cativeiro, que foram submetidas a três procedimentos laparoscópicos, com intervalo de 15 dias. Após a contenção física, uma associação de cetamina (25mg/kg) e midazolam (0,5mg/kg) foi administrada por via intramuscular para contenção química. Posteriormente, a anestesia foi induzida e mantida com isoflurano, e administrou-se aleatoriamente metadona (0,5mg/kg), tramadol (5mg/kg) ou placebo salina por via intramuscular. Após a contenção farmacológica e em estágio final da laparoscopia, foram obtidas amostras de sangue venoso para contagem sanguínea completa, proteína de plasma total (TP), creatinina, alanina aminotransferase (ALT), cálcio, sódio, potássio e cloreto ionizado. Durante a anestesia geral, a concentração de hemoglobina, TP e linfócitos diminuiu (P= 0,029;< 0,001; 0,022, respectivamente), enquanto os níveis de potássio aumentaram (P= 0,034). Em conclusão, a contenção química com associação de cetamina/midazolam promove uma ligeira diminuição dos componentes celulares do sangue. A anestesia com isoflavano para o procedimento laparoscópico levou a uma diminuição das concentrações de hemoglobina, linfócitos e proteínas, enquanto o potássio aumentou, sem qualquer influência do tratamento com tramadol ou metadona. No entanto, essas alterações foram transitórias, e os seus valores hematológicos obtidos podem colaborar na realização de estudos epidemiológicos, fisiopatológicos ou casuísticas para Cuniculus paca.*

*Palavras-chave: ecocardiografia, eletrocardiografia, roedores, neotropical, selvagem*

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## INTRODUCTION

Cuniculus paca, previously identified as Agouti paca, is the second largest rodent in South America, naturally found from Mexico to Argentina (Emmons *et al*., 2016), and their habitat destruction and hunting threatens wildlife maintenance (Chiarello *et al*., 2008). Trying to preserve the species, commercial breeding has been assembled, and biological studies propitiated, particularly in regard to clinical and reproductive characteristics (Lourenço *et al*., 2008). In this context, hematologic analyses are scarce in Cuniculus paca and only a few reference values have been published (Pachaly *et al*., 2001; Estrada *et al*., 2011; Stradiotti *et al*., 2015).

Due to the behavioral characteristics and great susceptibility to stress, chemical restraint and/or anesthesia are necessary for clinical procedures (Pachaly and Werner 1998), and for this reason it is important to define and characterize if these procedures cause hematologic alterations as described in other species (Marini *et al*., 1997; Kiliç, 2008). The aim of the study was to evaluate some hematological components in healthy female Spotted Pacas in captivity, that underwent laparoscopy under ketamine/midazolam chemical restraint, isoflurane anesthesia and tramadol or methadone treatment.

## MATERIAL AND METHODS

The animals were cared for in accordance with guidelines such as the Brazilian Council for Control of Animal Experimentation guidelines (available from http://dx.doi.org/10.1590/S0102-86502009000100015 [accessed on July10, 2017]), and their use of animals was reviewed and approved by institutional Ethics Committee (027420/11) and our Department was registered in the Institute of Environment and Renewable Natural Resources (IBAMA), as Brazilian fauna specimens' scientific purposes breeder (482508).

A prospective randomized cross-over blind clinical trial was conducted in eight(1±5 years) healthy female adults, adapted to captivity, in specialized confinements, identified by microchip and fed with rodents' dry food, fruits, vegetables and water. Each animal was subjected to the experimental protocol 3 times, with a 15 day interval.

On the day of the experiment, the animals were captured and physically restrained with a proper sized net. Immediately, the midazolam 0.5mg/kg (Dormonid®, Roche, São Paulo, Brazil) and ketamine 25mg/kg (Ketalar®, Pfizer, Itapevi, Brazil) association was administered intramuscularly (IM) in the thigh, for chemical restraint (CR). Once having lost postural reaction, the animals were transferred to the research center, placed in supine position and the fore limbs were shaved and disinfected for catheterization (over-the-needle catheter 22G) of the cephalic vein. Venous blood was collected by dripping and stored in purple and red tubes (0.5mL) for immediate analysis on an automatic complete blood counter (ABC vet counter®, Horiba, Northampton, United Kingdom), microscope differential leukocytes count, and measurement (BIO-2000 IL®, Bioplus, Barueri, Brazil) of total plasmatic protein (TP), serum creatinine, alanine amino transferase (ALT), sodium (Na), potassium (K), chloride (Cl), calcium free ionized fraction (iCa) and osmolality (Osm). This moment was identified as CR.

Subsequently, Ringer's lactate was infused at 10mL/kg/h, anesthesia induction and maintenance was achieved by isoflurane vaporization (in oxygen 100%; 0.2L/kg/min) in the concentration necessary to maintain the plane of surgical anesthesia (eyeball rotation, medium arterial pressure > 65mm Hg and absence of sensitivity) via face mask using a partial rebreathing circuit with the animals breathing spontaneously. Once on surgical plane, the animals were randomly chosen to receive IM tramadol 5mg/kg (TRA), methadone 0.5mg/kg (MET) or saline placebo 0.1mL/kg (CON), with the evaluators blinded to the treatment. After 15 minutes of stable plane of anesthesia, laparoscopic ovum pick-up (LOPU) was performed as described by Barros *et al*. (2016).

Once the LOPU ended, the blood sampling and analysis were repeated and this moment was identified as AS. At this moment, the animals in the CON group received tramadol 5mg/kg intravenously (IV), and 10 minutes later isoflurane was suspended. Oxygen inhalation was maintained for 10 minutes and IM penicillin 20.000IU/Kg, dihydrostreptomycin 2.0mg/kg (Penfort®, Ourofino, Cravinhos, Brazil) and meloxicam 0.3mg/kg (Maxicam®, Ourofino,

Cravinhos, Brazil) were administered. Subsequently, the animals were transferred to individual stalls until they recovered from anesthesia, and then were returned to collective enclosures and treated with IM meloxicam 0.2mg/kg every 24 hours for 3 days, using a pole syringe. Daily inspection was performed until complete recovery was deemed.

Statistical analysis was performed using the R software (R Foundation for Statistical Computing, Vienna, Austria), normality distribution of residuals (Shapiro-Wilk test) and homoscedasticity of variances (Barlett test) were tested. Real or transformed variables were compared between moments and analgesic treatments by repeated measures ANOVA and Tukey post-test (P< 0. 05).

## RESULTS

Cephalic vein catheterization had not been described before in the species. Although, not visible or palpable due to low skin elasticity, this vessel is located on the cranial face of the forelimb in the middle of a distance between the carpus and the elbow, and it was considered a simple, practical, safe and feasible technique for blood collection.

Values from the hematological analysis in Cuniculus paca under chemical restraint, general anesthesia and treated with tramadol, methadone or placebo are summarized in Table 1 and 2. Under general anesthesia, hemoglobin, TP and lymphocytes decreased (P= 0.029;< 0.001 and 0.022 respectively), whereas potassium levels increased (P= 0.034) when compared to the values during chemical restraint. None of the other studied parameters suffered anesthesia/analgesia influences (P> 0.05). When comparing inter-evaluation periods (15 days), all variables were similar (P> 0.05).

Table 1. Cellular and biochemical hematologyc components in female Cuniculus paca undergoing ketamine/midazolam chemical restraint and isofluorane anesthesia for laparoscopic ovum pick-up

| Variables | Chemical restraint | | | Anesthesia/surgery | | | P-Value |
|---|---|---|---|---|---|---|---|
| | Mean±SE | Range | n | Mean±SE | Range | n | |
| RBC $10^6$/µL | 4.08±0.13 | 3.01±5.45 | 24 | 3.77±0.10 | 2.63±4.87 | 24 | 0.056 |
| HGB g/dL | 12.1±0.33 | 7.60±15.6 | 24 | 11.1±0.29 | 6.80±12.9 | 24 | 0.029[a] |
| PVC % | 34.8±1.13 | 24.3±46.7 | 24 | 32.1±1.01 | 21.1±42.6 | 24 | 0.069 |
| MCV fL | 85.0±0.56 | 80.5±89.7 | 24 | 84.8±0.59 | 78.2±90.0 | 24 | 0.809 |
| MCH pg | 29.8±0.82 | 25.2±38.5 | 24 | 29.6±0.81 | 24.8±38.8 | 24 | 0.890 |
| MCHC g/dL | 35.1±1.02 | 29.5±45.0 | 24 | 35.0±1.04 | 28.4±45.8 | 24 | 0.903 |
| WBC $10^3$/µL | 8.97±0.91 | 4.80±21.4 | 24 | 7.15±0.57 | 3.70±13.6 | 24 | 0.100 |
| NE $10^3$/µL | 4.66±0.64 | 1.25±13.5 | 24 | 4.07±0.49 | 1.79±10.9 | 24 | 0.688 |
| LY $10^3$/µL/ | 3.65±0.40 | 1.08±11.1 | 24 | 2.55±0.21 | 0.59±5.50 | 24 | 0.022[a] |
| MO $10^3$/µL/ | 0.49±0.11 | 0.00±2.34 | 24 | 0.39±0.07 | 0.00±1.29 | 24 | 0.834 |
| EO $10^3$/µL/ | 0.16±0.04 | 0.00±0.72 | 24 | 0.11±0.02 | 0.00±0.39 | 24 | 0.289 |
| BA $10^3$/µL/ | 0.03±0.01 | 0.00±0.17 | 24 | 0.02±0.01 | 0.00±0.14 | 24 | 0.594 |
| BD $10^3$/µL/ | 0.00±0.00 | 0.00±0.00 | 24 | 0.01±0.01 | 0.00±0.06 | 24 | 0.343 |
| PL $10^3$/µL | 340±22,6 | 162±558 | 24 | 342±26,6 | 155±723 | 24 | 0.948 |
| TP mg/dL | 6.49±0.19 | 5.20±8.40 | 24 | 5.60±0.11 | 4.80±6.50 | 24 | <0.001[a] |
| ALT UI/L | 20.9±4.55 | 5.00±89.0 | 24 | 19.2±2.50 | 5.00±52.0 | 24 | 0.455 |
| CRE mg/dL | 1.23±0.04 | 1.00±1.60 | 24 | 1.29±0.05 | 0.90±1.80 | 24 | 0.285 |
| $Na^+$ mmol/L | 144±0.96 | 138±152 | 19 | 144±0.91 | 136±150 | 19 | 0.902 |
| $K^+$ mmol/L | 3.79±0.38 | 2.54±11.6 | 22 | 4.24±0.32 | 2.80±9.02 | 21 | 0.034[a] |
| $iCa^{++}$ mmol/L | 0.94±0.05 | 0.57±1.45 | 22 | 0.85±0.06 | 0.13 -1.35 | 21 | 0.201 |
| $Cl^{\pm}$mmol/L | 102±1.15 | 94.4±112 | 22 | 105±2.18 | 96.9±134 | 21 | 0.244 |
| Osm mmol/L | 287±1.69 | 273±296 | 19 | 287±1.79 | 275±299 | 19 | 0.974 |

Erythrocytes (RBC), hemoglobin (HGB), packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (WBC), neutrophils (NE), lymphocytes (LY), monocytes (MO), eosinophils (EO), basophils (BA), bands (BD), platelets (PL), creatinine (CRE), total plasma protein (TP), alanine amino transferase (ALT), sodium (Na+), potassium (K+), chloride (Cl-), ionized calcium (iCa++) and osmolality (Osm) blood concentrations. a significant level of 5%.

Table 2. Cellular and biochemical hematologyc components (Mean±SE) in female Cuniculus paca undergoing ketamine/midazolam chemical restraint, isofluorane anesthesia and treated with methadone (MET n= 8), tramadol (TRA n= 8) or placebo (CON n= 8) for laparoscopic ovum pick-up

| Variables | CON | TRA | MET | P-Value |
|---|---|---|---|---|
| RBC $10^6$/µL | 3.62±0.22 | 3.67±0.19 | 4.04±0.09 | 0.631 |
| HGB g/dL | 11.5±049 | 10.6±0.71 | 11.2±0.17 | 0.417 |
| PVC % | 30.6±2.19 | 31.4±1.90 | 34.4±0.59 | 0.644 |
| MCV fL | 84.1±1.13 | 85.2±1.22 | 85.2±0.76 | 0.772 |
| MCH pg | 32.2±1.81 | 28.8±1.31 | 27.9±0.34 | 0.136 |
| MCHC g/dL | 38.4±2.38 | 33.9±1.54 | 32.7±0.19 | 0.169 |
| WBC $10^3$/µL | 7.36±1.11 | 7.86±1.17 | 5.98±0.57 | 0.335 |
| NE $10^3$/µL | 4.54±1.17 | 4.59±0.82 | 3.09±0.29 | 0.489 |
| LY $10^3$/µL | 2.53±0.25 | 2.68±0.53 | 2.43±0.31 | 0.223 |
| MO $10^3$/µL | 0.39±0.14 | 0.42±0.14 | 0.37±0.08 | 0.382 |
| EO $10^3$/µL | 0.12±0.03 | 0.15±0.06 | 0.08±0.03 | 0.118 |
| BA $10^3$/µL | 0.04±0.02 | 0.03±0.02 | 0.02±0.01 | 0.293 |
| BD $10^3$/µL | 0.00±0.00 | 0.00±0.00 | 0.00±0.01 | 0.360 |
| PL $10^3$/µL | 408±66.6 | 308±20.4 | 310±34.0 | 0.200 |
| TP mg/dL | 5.53±0.32 | 5.70±0.29 | 5.60±0.21 | 0.334 |
| ALT UI/L | 21.9±3.63 | 13.9±2.9 | 21.8±5.8 | 0.425 |
| CRE mg/dL | 1.18±0.08 | 1.33±0.10 | 1.38±0.07 | 0.641 |
| $Na^+$ mmol/L | 145±1.53 | 143±1.61 | 144±1.61 | 0.708 |
| $K^+$ mmol/L | 4.13±0.82 | 4.10±0.52 | 4.48±0.28 | 0.115 |
| $iCa^{++}$ mmol/L | 0.68±0.09 | 0.09±0.08 | 0.87±0.11 | 0.453 |
| $Cl^{\pm}$mmol/L | 108±4.71 | 104±3.53 | 104±1.35 | 0.279 |
| Osm mmol/L | 286±1.90 | 285±3.19 | 289±2.89 | 0.706 |

Erythrocytes (RBC), hemoglobin (HGB), packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (WBC), neutrophils (NE), lymphocytes (LY), monocytes (MO), eosinophils (EO), basophils (BA), bands (BD), platelets (PL), creatinine (CRE), total plasma protein (TP), alanine amino transferase (ALT), sodium (Na+), potassium (K+), chloride (Cl-), ionized calcium (iCa++) and osmolality (Osm) blood concentrations.

## DISCUSSION

There were no anesthetic or surgical complications and all animals recovered satisfactorily. The blood cell counts in Pacas under chemical restraint were slightly lower than those reported in conscious (Estrada *et al*., 2011; Stradiotti *et al*., 2015) and sedated animals (Pachaly *et al*., 2001). This alteration may be related with ketamine and its associations since this causes reduction of the blood cells by sympathetic nervous system function modifications (Kiliç, 2008, Ahmed *et al*., 2009; Khalaf *et al*., 2014), or with the stress of blood sampling in conscious or sedated animals, which lead to splenic contraction (Thrall, 2012) and is related with a high lymphocytes count, reported by these authors (Table 3).

The Na, Cl, iCa and K concentrations were considered similar to those already reported in Cuniculus paca and other neotropical rodents (Pachaly *et al*., 2001; Corredor-Matus and Rodríguez-Pulido, 2012; Ribeiro *et al*., 2008).). Note that in our study the free ionized calcium fraction assessed has not been reported in such species, which in normal conditions corresponds to approximately 50% of the total calcium, as has been evaluated by same authors. We consider it important to describe that even our maximum K values in the MET group (4.5±0.8mmol/L) does not reach the levels (6.41±1.28mmol/L) reported as normal in Pacas by Pachaly *et al*. (2001).

Table 3. Cellular and biochemical histological components (Mean±SE) in Cuniculus paca undergoing ketamine/midazolam chemical restraint (n= 8, 3-times), compared with previous studies in conscious (Estrada *et al*., 2011, n= 20; Stradiotti *et al*., 2015, n= 11) and tranquilized animals (Pachaly *et al*., 2001, n= 12)

| Variables | Study results | Previous studies | | |
|---|---|---|---|---|
| | | A | B | C |
| RBC $10^6$/µL | 4.08±0.13 | 4.86±0.65 | NA | 4.61±0.18 |
| HGB g/dL | 12.1±0.33 | 15.1±1.37 | 12.0±0.25 | 13.4±0.36 |
| PVC % | 34.8±1.13 | 41.8±2.47 | 39,0±1.34 | 41.7±1.27 |
| MCV fL | 85.0±0.56 | 87.8±10.1 | NA | 92.0±3.60 |
| MCH pg | 29.8±0.82 | 32.1±13.5 | NA | 30.0±1,08 |
| MCHC g/dL | 35.1±1.02 | 37.0±3.12 | NA | 32.4±0.90 |
| WBC $10^3$/µL | 8.97±0.91 | 9.81±1.50 | 13,0±0.36 | 9.97±0.80 |
| NE $10^3$/µL | 4.66±0.64 | 3.39±0.77 | 1.56±0.36 | 4.01±0.85 |
| LY $10^3$/µL/ | 3.65±0.40 | 5.94±0.93 | 10.1±0.26 | 4.87±0.68 |
| MO $10^3$/µL/ | 0.49±0.11 | 0.16±0.06 | NA | 0.54±0.01 |
| EO $10^3$/µL/ | 0.16±0.04 | 0.33±0.13 | 1.30±0.08 | 0.32±0.01 |
| BA $10^3$/µL/ | 0.03±0.01 | NA | NA | 0.13±0.03 |
| BD $10^3$/µL/ | 0.00±0.00 | NA | NA | 0.34±0.03 |
| PL $10^3$/µL | 340±22,6 | NA | NA | NA |
| TP mg/dL | 6.49±0.19 | 6.27±0.45 | NA | NA |
| ALT UI/L | 20.9±4.55 | NA | NA | NA |
| CRE mg/dL | 1.23±0.04 | NA | 1.90±0.03 | NA |
| $Na^+$ mmol/L | 144±0.96 | 153±6.89 | NA | NA |
| $K^+$ mmol/L | 3.79±0.38 | 6.63±0.43 | NA | NA |
| $Ca^{++}$ mmol/L[a] | 0.94±0.05 | 3.63±0.07 | NA | NA |
| $Cl^{\pm}$mmol/L | 102±1.15 | NA | NA | NA |
| Osm mmol/L | 287±1.69 | NA | NA | NA |

A: Pachaly *et al*. (2001); B: Estrada *et al*. (2011); C: Stradiotti *et al*. (2015); [a]Our results were referent to iCa++, different of total Ca++ evaluated by previous studies. NA not available data. Erythrocytes (RBC), hemoglobin (HGB), packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (WBC), neutrophils (NE), lymphocytes (LY), monocytes (MO), eosinophils (EO), basophils (BA), bands (BD), platelets (PL), creatinine (CRE), total plasma protein (TP), alanine amino transferase (ALT), sodium (Na+), potassium (K+), chloride (Cl-), ionized calcium (iCa++) and osmolality (Osm) blood concentrations.

The anesthetic/laparoscopic procedure led to approximately 8% hemoglobin, TP and lymphocytes decrease. This effect may be explained by different mechanisms: 1) oxidative stress induced by isoflurane, leading to hemolysis and lymphopenia (Deckardt *et al*., 2007); 2) blood cell sequestration on hematopoietic organs, also attributed to isoflurane (Marini *et al*., 1997); or 3) surgical hemorrhage, iatrogenic hemodilution or water movement between body compartments (Kiliç, 2008). We believed that blood cell sequestration is the most plausible explanation for these hematological alterations, since acute hemolysis would probably lead to an unobserved HCM and CMHC increase (Thrall, 2012) and during the surgical procedure there was no apparent bleeding episode or a potential fluid overload. Another alteration resulting from this procedure was a rise in blood K, probably associated to respiratory acidosis reported in anesthetized rodents submitted to laparoscopy (Fuentes *et al*., 2004).

It's important to note that all of these hematological alterations appeared to be transient, since after the 15 day inter-experimental period, the evaluated parameters were similar to the baseline, as described by Inada *et al*. (2004) due to autonomic nervous or immune systems function imbalances and with limited clinical relevance.

In conclusion, chemical restraint with ketamine/midazolam association causes a slight decrease in blood cellular components.

Isoflurane anesthesia for laparoscopic procedure lead to decrease in hemoglobin, lymphocytes and protein concentrations, while potassium increased, without any influence from the analgesic treatment with tramadol or methadone. However, these alterations were transient, and these hematologic values can collaborate in carrying out epidemiological, pathophysiological or case studies in the Cuniculus paca.

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