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Gilberto Serighelli Júnior
Amanda Boeno Riva
Daniel Sérgio Cipriani
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Gabriela Borges Conterno
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Evaluation of antinociceptive and sedative effects of methadone or morphine in combination with ketamine-midazolam in *Oryctolagus cuniculus* (*Linnaeus*, 1758; European rabbits) undergoing elective orchiectomy

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Gilberto Serighelli Júnior[1], Amanda Boeno Riva[2], Daniel Sérgio Cipriani[2], Kelly Mota Fernandes[2], Gabriela Borges Conterno[3], Vanessa Arnaud Rocha[3], Samuel Jorge Ronchi[4], Maria Carolina de Souza[2], Felipe Comassetto[5], Aury Nunes de Moraes[5]*

[1]*M.Sc., Veterinary Sciences Graduate Program, Department of Veterinary Medicine, Federal University of Paraná, Curitiba, Brazil, State of Paraná, Brazil. ORCID:0000-0002-0979-7939*
[2]*Self-employed Veterinarian, State of Santa Catarina, Brazil. ORCID: 0009-0004-2757-7288; ORCID: 0000-0001-6404-6401; ORCID: 0009-0004-5539-5094*
[3]*M.Sc. Self-employed Veterinarian, State of Santa Catarina, Brazil. ORCID: 0000-0002-1256-4677;*
[4] *Dr. Self-employed Veterinarian, State of Santa Catarina, Brazil. ORCID: 0000-0003-0556-6006*

Author for correspondence:

Gilberto Serighelli Júnior

gilberto.serighelli@ufpr.br

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ABSTRACT

The objective of this study was to evaluate the effect of adding methadone or morphine to an anesthetic protocol in combination with ketamine and midazolam in 24 rabbits undergoing elective orchiectomy. The animals, weighing 3.909±0.6693 kg, were evenly distributed into three groups, receiving 15 mg/kg of ketamine and 2 mg/kg of midazolam (GCON), associated with 2 mg/kg of methadone (GMET) or morphine (GMOR), intramuscularly.

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ABSTRACT

Cardiorespiratory parameters, blood gas analysis, and sedation degree were recorded at baseline (T-15), 15 minutes after premedication (T0), 5 minutes after local block (T1); clamping of the first spermatic cord (T2); second (T3), and immediately after scrotorraphy (T4). Sedation degree was assessed via posture (PS), resistance to dorsal recumbency (RD), jaw tone (JT), palpebral reflex (PR), total sedation score (TS), muscle relaxation (MR), and stimuli response (RS).

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ABSTRACT

The inclusion of a μ-agonist opioid enhanced the degree of sedation without negatively affecting anesthetic recovery. Results showed that methadone provided deeper sedation and greater respiratory depression, while morphine had a similar but less pronounced effect. GMET exhibited a significant reduction in respiratory rate ($p<0.0001$) and an increase in $PaCO_2$ ($p<0.0001$), indicating more pronounced respiratory depression compared to the other groups.

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HR remained within normal limits for GMOR and GMET, whereas GCON showed a significant increase (p=0.0221). No significant changes in blood pressure were observed between groups. The sedation degree was significantly higher in GMET compared to GCON (p=0.0018).

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ABSTRACT

It is concluded that opioids improved sedation degree without compromising cardiovascular stability, though oxygen therapy was required due to respiratory depression, particularly with methadone.

Keywords: anesthesiology, lagomorphs, nociception, opioids, sedation.

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	Groups	Time points					
		T-15	T0	T1	T2	T3	T4
HR (bpm)	GCON	213.4 ± 31	277.3 ± 23A	267.4 ± 28A	277.8 ± 21Aa	273.6 ± 39Aa	263.8 ± 33Aa
	GMOR	239.4 ± 30	265.1 ± 36	251.6 ± 23	245.1 ± 26ab	245.1 ± 24ab	237.9 ± 22ab
	GMET	250.1 ± 35	281.4 ± 15	233.1 ± 46	239.1 ± 36b	219.5 ± 36b	217.9 ± 36b
RR (mpm)	GCON	131.8 ± 56	60.3 ± 42A	50.3 ± 16Aa	62.0 ± 16Aa	65.3 ± 33Aa	71.1 ± 19Aa
	GMOR	168.5 ± 41	66.5 ± 44A	32.5 ± 13Ab	37.5 ± 26Aab	35.5 ± 15Ab	47.5 ± 40Ab
	GMET	168.8 ±62	47.0 ± 28A	16.8 ± 09Ab	19.5 ± 16Ab	15.8 ± 11Ab	23.3 ± 15Ab
SpO_2 (%)	GCON	92.6 ± 02	88.0 ± 03Aa	98.9 ± 01Aa	97.0 ± 03	97.1 ± 03A	98.3 ± 03A
	GMOR	92.6 ± 03	88.4 ± 05a	96.8 ± 04a	95.4 ± 06	97.3 ± 02A	96.1 ± 05
	GMET	93 ± 04	78.4 ± 09Ab	86.9 ± 09b	95.5 ± 04	95.9 ± 04	97.3 ± 03
SAP (mmHg)	GCON	107.1 ± 17	103.5 ± 11	100.6 ± 10	103.4 ± 11	104.8 ± 13	100.3 ± 10
	GMOR	99.0 ± 13	102.5 ± 18	88.4 ± 16	91.4 ± 15	95.4 ± 14	94.1 ± 14
	GMET	104 ± 10	92.6 ± 12	103.3 ± 20	106.3 ± 19	98.5 ± 08	97.6 ± 14
DAP (mmHg)	GCON	90.0 ± 14	88.8 ± 08	86.9 ± 10	92.6 ± 08	91.4 ±12	86.5 ± 12
	GMOR	76.9 ± 14	79.8 ± 16	70.0 ± 15	72.9 ± 18	77.0 ± 15	72.9 ± 12
	GMET	85.1 ± 07	73.4 ± 12	84.3 ± 19	83.4 ± 19	79.8 ± 09	73.8 ± 15
MAP (mmHg)	GCON	95.0 ± 10	95.1 ± 08	91.1 ± 11	97.6 ± 09	96.6 ± 12	90.6 ± 08
	GMOR	83.5 ± 12	88.0 ± 17	78.1 ± 13	79.5 ± 17	84.1 ± 15	81.1 ± 12
	GMET	93.1 ± 07	80.1 ± 11	93.3 ± 20	93.9 ± 20	88.0 ± 08	81.3 ± 14
RT (°C)	GCON	38.7 ± 0.8	38.9 ± 0.9	39.2 ± 0.5	39.1 ± 0.5	39.0 ± 0.6	39.0 ± 0.6
	GMOR	39.2 ± 0.6	39.2 ± 0.6	39.3 ± 0.5	39.1 ± 0.6	38.8 ± 0.7	38.6 ± 0.7
	GMET	38.7 ± 0.5	39.2 ± 0.8	39.0 ± 0.2	38.8 ± 0.3	38.6 ± 0.3	38.4 ± 0.5

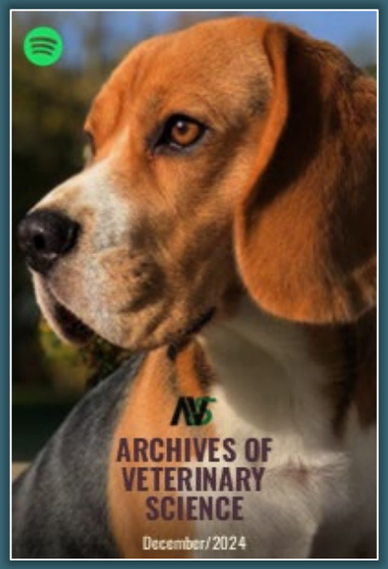

Table 1 – Mean values and standard deviations of the cardiorespiratory parameters analyzed (heart rate - HR; partial oxygen saturation of hemoglobin - SpO2; respiratory rate - RR; systolic arterial pressure - SAP, mean arterial pressure - MAP, and diastolic arterial pressure - DAP; and rectal temperature - RT) in rabbits subjected to an anesthetic protocol composed of ketamine and midazolam (GCON); ketamine, midazolam, and morphine (GMOR); or ketamine, midazolam, and methadone (GMET), for elective orchiectomy (T-15 - baseline; T0 - 15 minutes after protocol administration; T1 - 5 minutes after local block; T2 - clamping of the first spermatic cord; T3 - clamping of the second spermatic cord; and T4 - immediately after scrotorraphy).

Obs: Uppercase letters within rows for the same variable indicate a difference in relation to the baseline moment (T-15). Lowercase letters within rows for the same variable in the same column indicate a difference between groups at the same time point.

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	Groups	Time points			
		T-15	T0	T2	T4
pH	GCON	7.32 ± 0.17	7.38 ± 0.14	7.36 ± 0.09	7.38 ± 0.07
	GMOR	7.44 ± 0.07	7.43 ± 0.03	7.33 ± 0.03A	7.36 ± 0.05A
	GMET	7.40 ± 0.05	7.39 ± 0.03	7.27 ± 0.11	7.24 ± 0.19
PaO_2 (mmHg)	GCON	75.1 ± 10	62.1 ± 04Aa	389.8 ± 69A	405.1 ± 47A
	GMOR	78.2 ± 07	58.4 ± 05Aa	414.0 ± 56A	344.1 ± 177A
	GMET	81.6 ± 05	48.5 ± 07Ab	329.6 ± 100A	294.0 ± 134A
$PaCO_2$ (mmHg)	GCON	35.1 ± 09a	38.9 ± 03A	43.7 ± 04Aa	41.2 ± 04a
	GMOR	28.9 ± 03ab	37.3 ± 03A	53.6 ± 05Aab	49.8 ± 05Aab
	GMET	27.7 ± 02b	39.7 ± 04A	67.3 ± 23Ab	75.7 ± 40Ab
SO_2c (%)	GCON	90.8 ± 10.3	90.0 ± 5.5a	99.9 ± 0.1	99.9 ± 0.1
	GMOR	95.8 ± 0.9	90.6 ± 2.3Aa	99.9 ± 0.1A	98.7 ± 2.4A
	GMET	95.6 ± 0.8	82.2 ± 6.1Ab	98.7 ± 2.2A	98.9 ± 1.9A
HCO_3^- (mmol L^{-1})	GCON	18.61 ± 6.33	23.61 ± 6.74A	24.46 ± 3.92Aa	24.20 ± 4.20A
	GMOR	19.61 ± 3.85	24.44 ± 2.57A	27.93 ± 3.37Aab	28.06 ± 3.41A
	GMET	16.95 ± 2.51	23.40 ± 2.14A	29.03 ± 2.47Ab	28.80 ± 4.81A
BEc (mmol L^{-1})	GCON	- 7.28 ± 8.56	- 1.48 ± 8.85A	- 0.93 ± 5.20	- 0.90 ± 5.22A
	GMOR	- 4.46 ± 4.80	0.20 ± 2.95A	2.06 ± 3.76A	2.75 ± 3.93A
	GMET	- 7.84 ± 3.26	- 1.58 ± 2.36A	1.95 ± 1.90A	1.41 ± 4.84A
Na^+ (mmol L^{-1})	GCON	142.60 ± 3.49	142.30 ± 2.10	141.70 ± 1.52a	141.30 ± 1.60a
	GMOR	144.70 ± 2.51	144.40 ± 2.85	145.00 ± 2.31b	144.90 ± 1.56b
	GMET	144.60 ± 2.18	144.20 ± 1.70	145.40 ± 2.40b	145.00 ± 1.70b
K^+ (mmol L^{-1})	GCON	4.07 ± 0.44a	3.60 ± 0.31A	3.50 ± 0.48Aa	3.24 ± 0.35A
	GMOR	3.55 ± 0.23b	3.35 ± 0.37	3.14 ± 0.16Ab	3.19 ± 0.22A
	GMET	3.70 ± 0.22b	3.58 ± 0.24	3.32 ± 0.21Aab	3.30 ± 0.33A
Ca^{++} (mmol L^{-1})	GCON	1.28 ± 0.14	1.25 ± 0.20	1.25 ± 0.19	1.18 ± 0.06
	GMOR	1.16 ± 0.11	1.22 ± 0.22	1.32 ± 0.10A	1.29 ± 0.12A
	GMET	1.17 ± 0.13	1.13 ± 0.14	1.15 ± 0.17	1.19 ± 0.10
Cl^- (mmol L^{-1})	GCON	104.80 ± 3.38	103.60 ± 2.83	103.10 ± 1.43	103.30 ± 1.86
	GMOR	107.80 ± 2.15	106.00 ± 3.14	105.10 ± 1.83A	105.20 ± 1.56A
	GMET	107.30 ± 1.83	105.60 ± 1.77A	105.20 ± 2.04A	104.70 ± 1.67A
AG (mmol L^{-1})	GCON	23.26 ± 5.52	18.66 ± 6.19A	17.66 ± 3.02A	17.01 ± 2.90A
	GMOR	20.79 ± 3.94	17.29 ± 1.69A	15.13 ± 1.97A	14.85 ± 1.93A
	GMET	24.01 ± 3.34	18.88 ± 1.67A	14.60 ± 2.32A	14.85 ± 3.84A

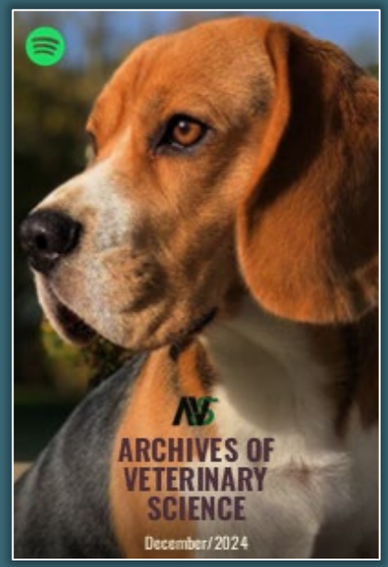

Table 2 – Mean values and standard deviations of the arterial blood gas parameters analyzed (hydrogen potential - pH; arterial oxygen pressure - PaO_2; arterial carbon dioxide pressure - $PaCO_2$; corrected oxygen saturation - SO_2c; bicarbonate - HCO_3^- corrected base excess - BE; sodium - Na^+; potassium - K^+; ionized calcium - Ca^{++}; chloride - Cl^-, and anion gap - AG) in rabbits subjected to an anesthetic protocol composed of ketamine and midazolam (GCON); ketamine, midazolam, and morphine (GMOR); or ketamine, midazolam, and methadone (GMET) for elective orchiectomy (T-15 - baseline; T0 - 15 minutes after protocol administration; T2 - clamping of the first spermatic cord, and T4 - immediately after scrotorraphy).

Obs: Uppercase letters within rows for the same variable indicate a difference in relation to the baseline moment (T-15), after analysis by Repeated Measures One-way ANOVA followed by Dunnett's test ($p < 0.05$). Lowercase letters within rows for the same variable in the same column indicate a difference between groups at the same time point.

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	Groups	Time points				
		T0	T1	T2	T3	T4
PS	GCON	4 [3-5]	4.5 [3-5]	4 [3-5]	4 [3-5]a	4 [3-5]a
	GMOR	4.5 [4-5]	4.5 [4-5]	5 [5-5]	5 [4-5]	4.5 [4-5]
	GMET	4.5 [4-5]	5 [5-5]	5 [5-5]	5 [5-5]b	5 [5-5]b
RD	GCON	2 [1-3]	2.5 [1-3]	2 [1-3]	2 [1-3]a	2 [1-3]
	GMOR	3 [2-3]	3 [3-3]	3 [3-3]	3 [2-3]	3 [2-3]
	GMET	3 [2-3]	3 [3-3]	3 [3-3]	3 [3-3]b	3 [3-3]
JT	GCON	0 [0-1]	0.5 [0-1]	0 [0-1]	0 [0-1]	0 [0-1]
	GMOR	0 [0-0]	0.5 [0-1]	0.5 [0-1]	0.5 [0-1]	0.5 [0-1]
	GMET	0 [0-1]	1 [0-1]	1 [0-1]	1 [0-1]	1 [0-1]
PR	GCON	1 [0-2]	1 [0-2]	1 [0-2]	1 [0-2]a	1 [0-1]
	GMOR	1 [0-1]	1 [1-2]	1 [1-2]	1 [1-2]	1 [1-2]
	GMET	1 [0-2]	2 [1-2]	2 [1-2]	2 [2-2]b	2 [1-2]
TS	GCON	7.5 [5-11]	9.5 [4-11]	8 [4-9]a	7 [4-9]a	8.5 [5-13]a
	GMOR	8 [6-9]	9 [9-11]	9.5 [9-11]	9.5 [7-11]	9 [7-11]
	GMET	8.5 [7-10]	11 [9-11]	11 [10-11]b	11 [10-11]b	11 [9-11]b
MR	GCON	-	-	1 [1-3]a	1 [0-2]a	1,5 [1-3]
	GMOR	-	-	3 [3-3]b	3 [2-3]b	3 [2-3]
	GMET	-	-	3 [3-3]b	3 [3-3]b	3 [3-3]
RS	GCON	-	-	1.5 [1-2]a	0.5 [0-2]a	1.5 [1-2]a
	GMOR	-	-	3 [3-3]b	2.5 [2-3]b	2.5 [1-3]b
	GMET	-	-	3 [3-3]b	3 [3-3]b	3 [3-3]b

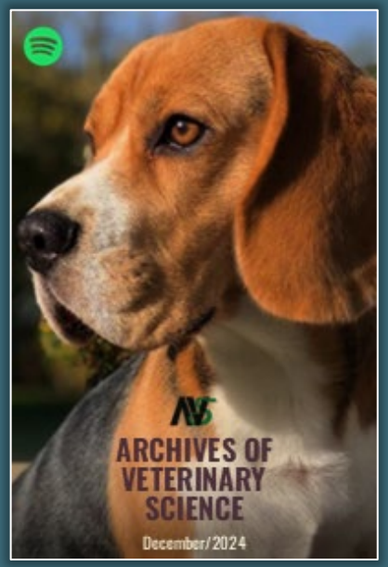
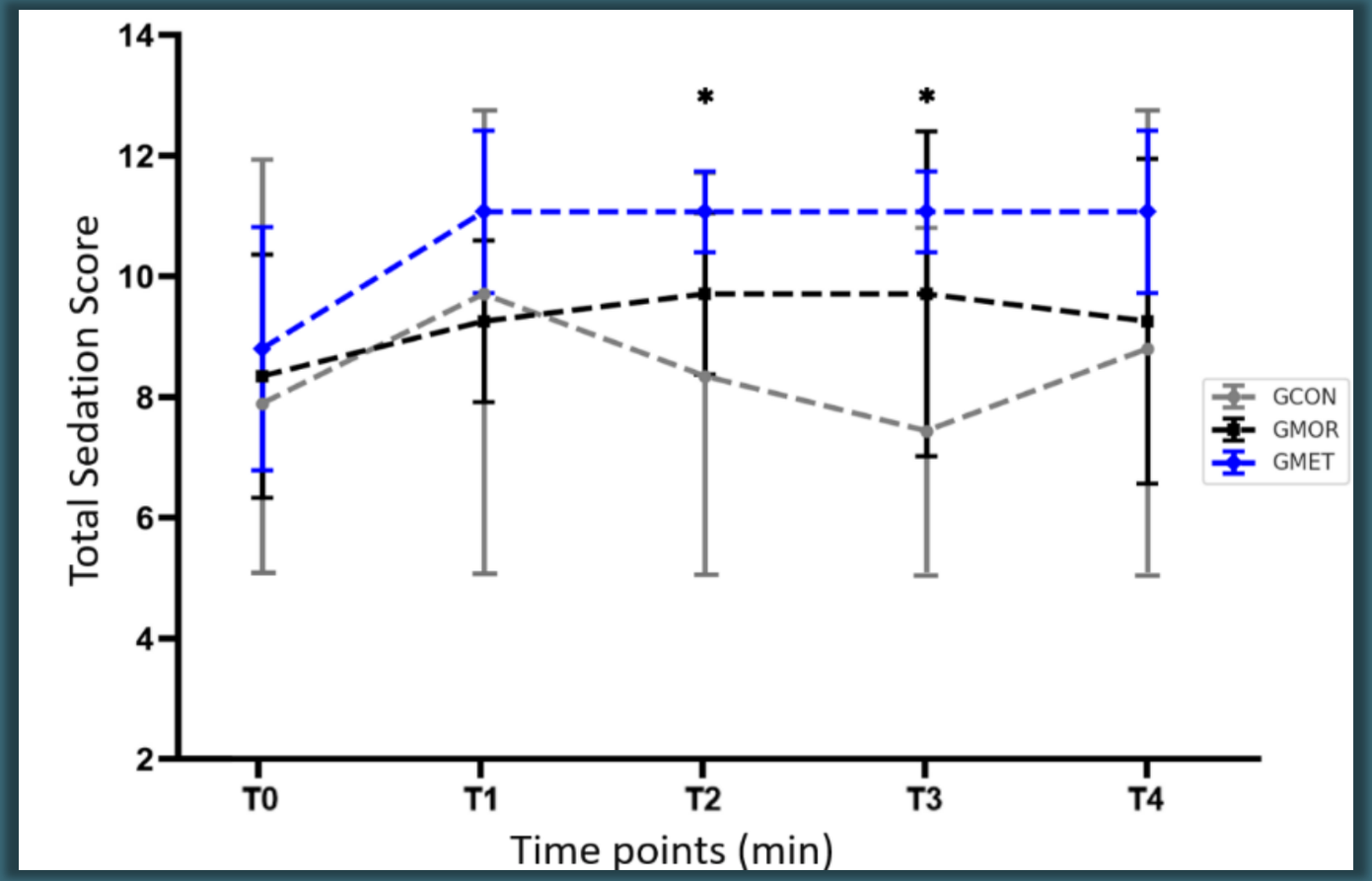


Table 3 – Total score sedation (median) followed by the maximum and minimum values of the scores obtained using the sedation scale proposed by Bellini et al. (2014) (posture - PS; resistance to dorsal recumbency - RD; jaw tone - JT; palpebral reflex - PR, and total sedation score - TS) and using the sedation scale adapted from Comasseto et al. (2014) (muscle relaxation - MR and response to stimuli - RS) in rabbits subjected to an anesthetic protocol composed of ketamine and midazolam (GCON); ketamine, midazolam, and morphine (GMOR); or ketamine, midazolam, and methadone (GMET). For elective orchiectomy (T0 - 15 minutes after protocol administration; T1 - 5 minutes after local block; T2 - clamping of the first spermatic cord; T3 - clamping of the second spermatic cord, and T4 - immediately after scrotorraphy).

Obs: Lowercase letters within rows for the same variable in the same column indicate a difference between groups at the same time point.



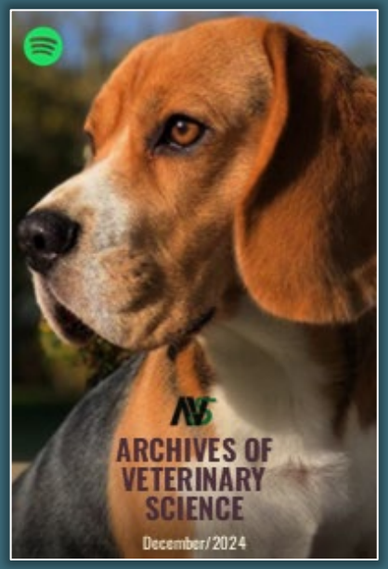


Figure 1 – Total sedation score (median) followed by the respective standard deviations, maximum and minimum values of the scores obtained by summing the subitems of the sedation scale proposed by Bellini et al. (2014) (posture - PS; resistance to dorsal recumbency - RD; jaw tone - JT; palpebral reflex - PR) in rabbits subjected to an anesthetic protocol composed of ketamine and midazolam (GCON); ketamine, midazolam, and morphine (GMOR); or ketamine, midazolam, and methadone (GMET) for elective orchiectomy (T0 - 15 minutes after protocol administration; T1 - 5 minutes after local block; T2 - clamping of the first spermatic cord; T3 - clamping of the second spermatic cord; and T4 - immediately after scrotorraphy).
Obs: * Indicates a difference between GMET and GCON at the same time point.

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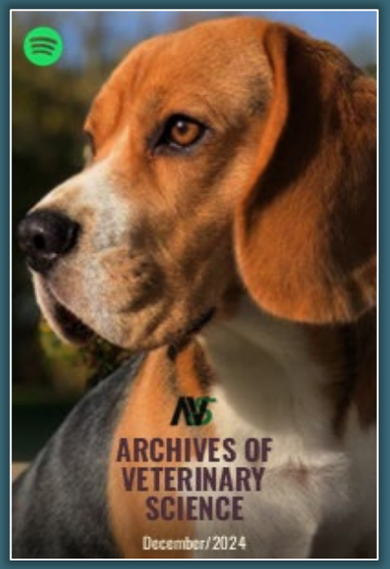

Extra Materials

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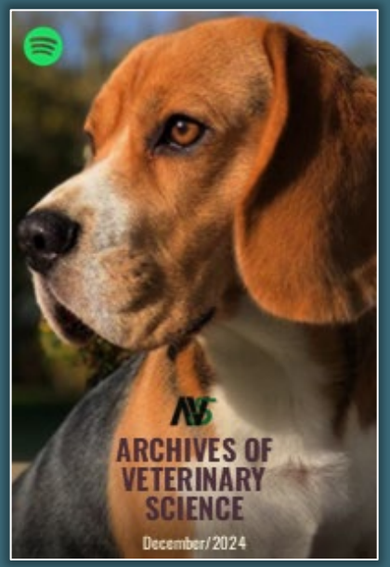

(A) Physical restraint using a towel; the arrow indicates the trichotomy of both ears for arterial and venous access. (B) Placement of a peripheral catheter in the marginal ear artery for arterial access.

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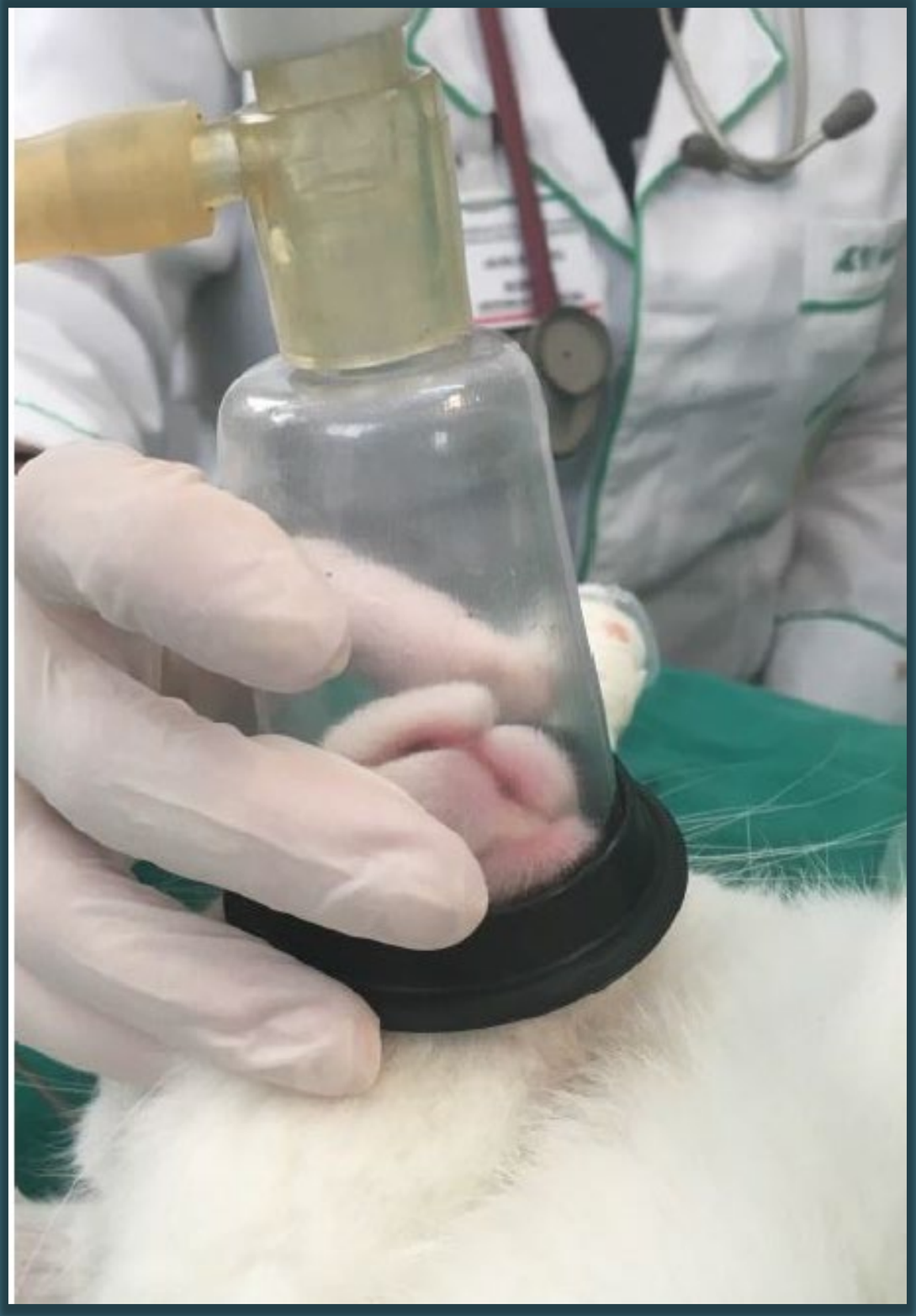

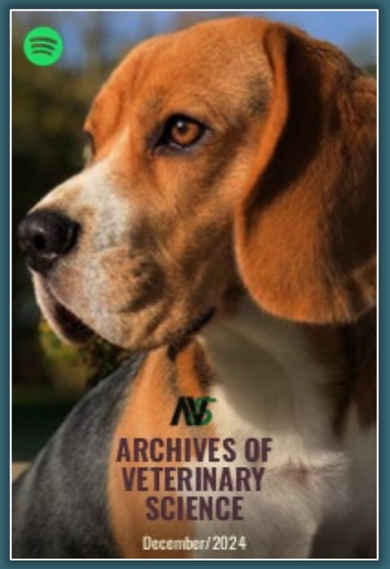

Supplementation of 100% oxygen supplementation via a facial mask in a rabbit undergoing an elective orchiectomy procedure.

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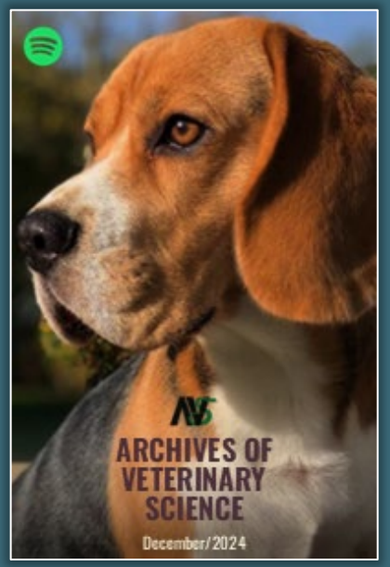
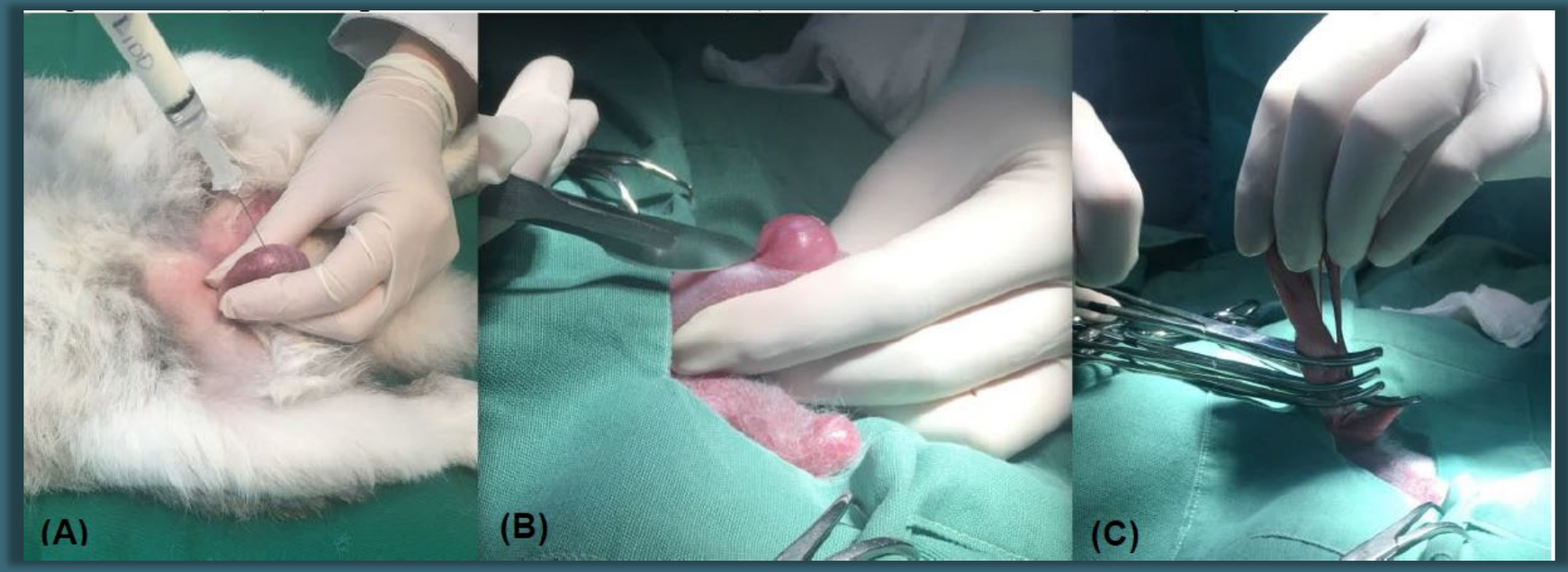
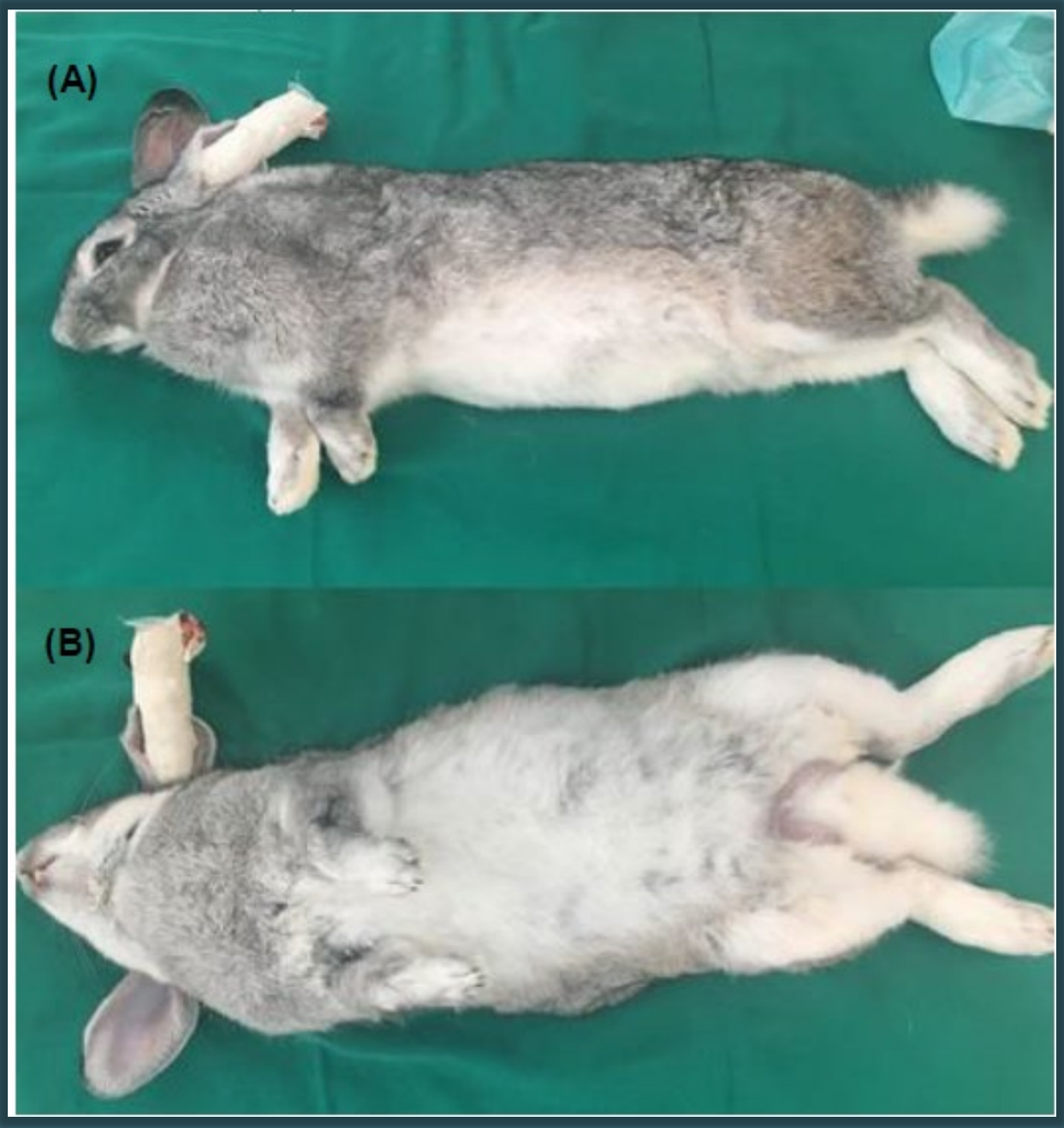
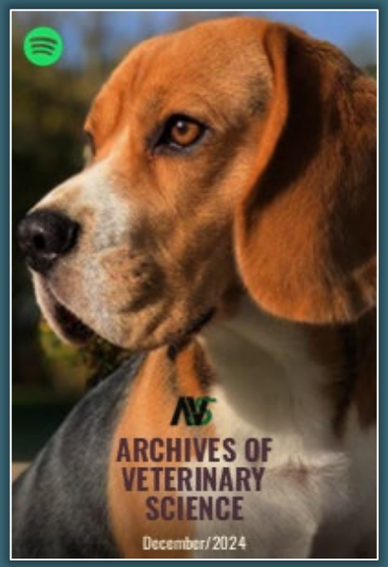




(A) Intratesticular block; (B) Initiation of the surgical procedure; (C) Testicular clamping.





Posture assessment using the Sedation Scale by Bellini et al. (2014) in rabbits. following treatment administration; (A) lateral recumbency in a rabbit; (B) no resistance to dorsal rolling.

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1973 - 2023

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CONCLUSION

The inclusion of μ-agonist opioids in the anesthetic protocol with ketamine and midazolam demonstrated a significant improvement in the quality of sedation in rabbits without compromising anesthetic recovery or the main cardiovascular parameters, such as heart rate, systolic, diastolic, and mean arterial pressure, as well as rectal temperature and electrolyte balance.

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Specifically, methadone caused more pronounced respiratory depression than morphine, resulting in hypoxemia and respiratory acidosis, as evidenced by significant alterations in respiratory rate, SpO_2, $PaCO_2$, PaO_2, and SO_2c. Therefore, 100% oxygen supplementation during the anesthetic period is necessary for this species and should ideally begin as soon as the animal allows for the proper fixation of the oxygenation mask or other oxygen therapy devices.

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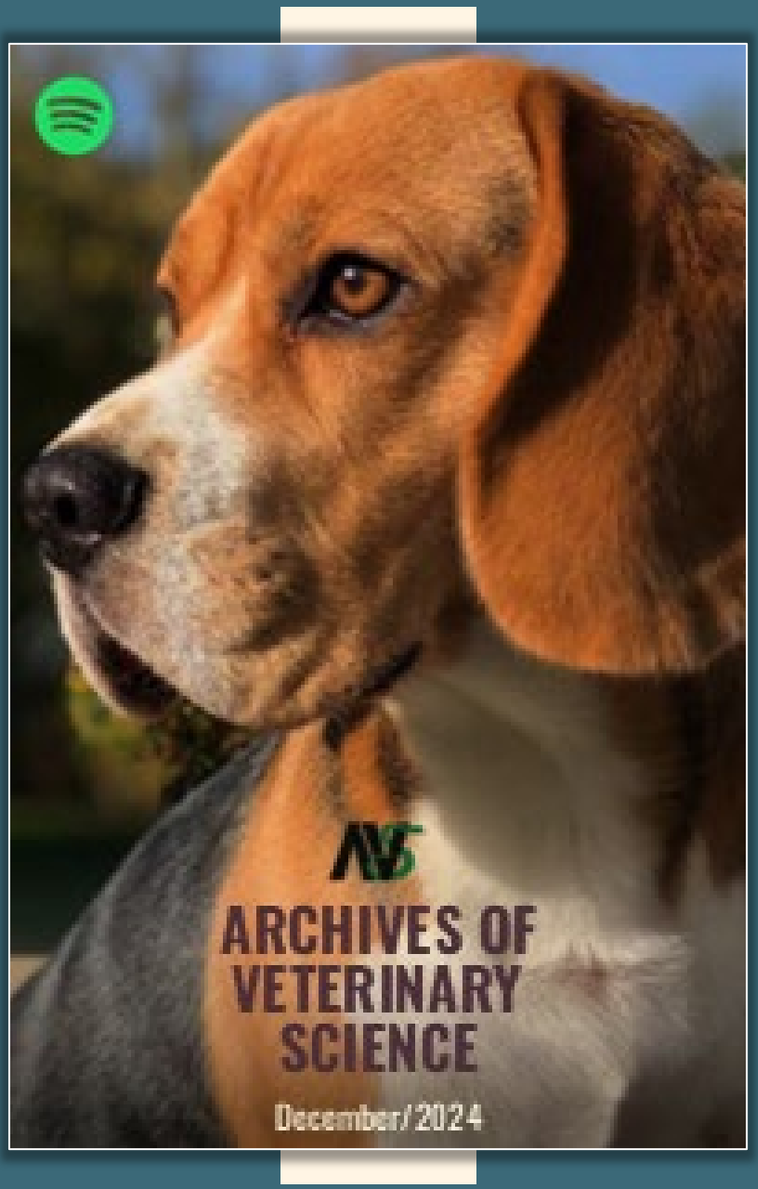

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