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Premedication with acetazolamide: Is its use for postoperative pain and stress control after laparoscopic ovariectomy in dogs ruled out?

Inês T. Tavares[1] | Ramón Rivero[2] | José P. Sales-Luís[3] | Carlo G. Vaudano[4] | Sérgio D. Correia[5,6] | Juan Alberto Corbera[7] | Jose Raduan Jaber[8]

[1]Faculty of Veterinary Medicine, Lusófona University, Lisbon, Portugal

[2]Faculty of Veterinary Medicine, Universidad Autónoma de Ciudad Juárez, Ciudad Juarez, México

[3]Faculty of Veterinary Medicine, Universidade de Lisboa, Avenida da Universidade Tecnica, Lisbon, Portugal

[4]Oeiras Veterinary Hospital, Oeiras, Paço de Arcos, Portugal

[5]COPELABS, Departamento de Arquitetura, Universidade Lusofóna de Humanidades e Tecnologias, Lisbon, Portugal

[6]VALORIZA, Centro de Investigação para a Valorização de Recursos Endógenos, Polytechnic Institute of Portalegre, Portalegre, Portugal

[7]Hospital Clínico Veterinario ULPGC, Facultad de Veterinaria, Instituto Universitario de Investigaciones Biomédicas y Sanitarias, Universidad de Las Palmas de Gran Canaria, Arucas, Spain

[8]Facultad de Veterinaria, Departamento de Morfología, Universidad de Las Palmas de Gran Canaria, Arucas, Spain

Correspondence
Email: juan.corbera@ulpgc.es

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Abstract

Background: Studies in human medicine have concluded that acetazolamide reduces pain associated with carbon dioxide insufflation during laparoscopic surgery. However, there are no published reports regarding the use of acetazolamide for this purpose in companion animals, despite the increasing popularity of laparoscopic techniques in veterinary medicine due to their advantages over open surgeries.

Objectives: Thirty mixed-breed female dogs were included in the study and randomly assigned to one of three groups: OVE (median celiotomy ovariectomy; $n = 10$), OVEL (laparoscopic ovariectomy, $n = 10$) and OVELA (laparoscopic ovariectomy with acetazolamide preoperative administration; $n = 10$). Experienced surgeons performed all procedures, and the anaesthetic and analgesic protocols were identical for all animals. Acetazolamide was administered orally (at a dose of 25 mg/kg) 2 h prior to induction in the OVELA group. Postoperative pain was evaluated using serum cortisol, salivary cortisol, and the University of Melbourne Pain Scale (UMPS) Score.

Results: Any statistical differences were observed in the UMPS scores when the OVELA group was compared to the OVEL group at 1 h after surgery ($p = 0.515$), 12 h ($p = 0.375$) and 24 h ($p = 0.242$). Animals undergoing open surgery (OVE group) had significantly higher pain scores at all times after surgery when compared with OVEL and OVELA groups. A high positive correlation ($r = 0.792$; $p = 0.01$) was found between serum and saliva cortisol concentrations. Mean saliva cortisol concentration was not significantly lower for the OVELA group compared to the other groups.

Conclusions: This study found evidence that preoperative administration of acetazolamide may be beneficial in managing postoperative pain in dogs after laparoscopic surgeries. However, further research with a larger sample size is needed to confirm this and to determine if acetazolamide should be included in a multimodal postoperative analgesia protocol for laparoscopic ovariectomy in dogs.

KEYWORDS
acetazolamide, carbon dioxide, dog, laparoscopic ovariectomy, multimodal analgesia, pain assessment, pain scale, pneumoperitoneum, University of Melbourne Pain Scale

1 | INTRODUCTION

One of the most frequent procedures carried out in veterinary practice is elective sterilisation of dogs (Mayhew & Brown, 2007). Laparoscopic ovariectomy is a technique with several benefits and is safe and reliable in dogs (Van Goethem et al., 2003; Van Nimwegen et al., 2005; Wenkel et al., 2005; Cicirelli et al., 2022; Radford et al., 2021; Leonardi et al., 2020; Tavares et al., 2021).

Laparoscopic postoperative pain is associated with phrenic nerve neurapraxia, which is secondary to abdominal distension and the intraabdominal temperature, humidity, and amount of residual gas (Mouton et al., 1999). The number of cannulas used, the type of surgical procedure, and the surgeon's experience also influence the severity of postoperative pain (Leggett et al., 2000). The recommended approach to postoperative pain management in small animals is multimodal and uses several medications to act in different modes and sites (Epstein et al., 2015; Lamont, 2008). In laparoscopic procedures, carbon dioxide (CO_2) diffuses into tissues. It is absorbed into the systemic circulation through the peritoneum, which results in a decrease in peritoneal and plasma pH from the liberation of hydrogen ions, which can be responsible for some degree of pain (Bergström et al., 2008; Liem et al., 1996; Woehlck et al., 2003). Multiple techniques have been investigated to reduce or prevent the changes in intraperitoneal pH, such as the use of heating, humidification, bicarbonate, intraperitoneal lavage, gasless laparoscopy, and use of helium as a substitute for CO_2, all with mixed results (Wong et al., 2004; Neuhaus et al., 2000; Neuhaus et al., 2001; Dorrance et al., 1999; Farrell et al., 2000; Gupta et al., 2002; Watson et al., 1997).

The enzyme carbonic anhydrase speeds up the generation of carbonic acid (Woehlck et al., 2003). Acetazolamide (2-acetylamino-1,3,4-thiadiazole-5-sulphonamide) is a carbonic anhydrase inhibitor utilised in both human and veterinary medicine (Alberts et al., 2000). Acetazolamide is used for glaucoma therapy since it reduces the aqueous humour production in the ciliary body (Maślanka, 2015 Mar 1); however, its uses in cats are limited due to its systemic toxicity (McLellan & Miller, 2011). Acetazolamide has also been used to aid in the treatment of mild congestive heart failure in dogs (Shields, 2009), to reduce cerebrospinal fluid production, and consequently, as an adjuvant treatment of hydrocephalus, hydranencephaly and porencephaly (Kolecka et al., 2015), to treat idiopathic intracranial hypertension in humans (Supuran, 2015), for prophylactic treatment of hyperkalaemic periodic paralysis, a heritable equine muscle disease (Alberts et al., 2000) and udder oedema in cattle (Vestweber et al., 1989).

Acetazolamide potentially has a role in inhibiting both the membrane-bound and the cytoplasmic forms of carbonic anhydrase, which slows down enzymatic catalysis's production of H^+ ions (Bala et al., 2015). By inhibiting the carbonic anhydrase, the carbonic acid is possibly removed by diffusion or blood flow at a speed able to decrease painful stimulation (Woehlck et al., 2003). Studies conducted in human medicine have concluded that acetazolamide reduces pain related to carbon dioxide insufflation following laparoscopic surgery (Bala et al., 2015; Pourladian et al., 2016; Figueroa-Balderas et al., 2013; Nyerges, 1994). In dogs, the peritoneal fluid changes due to CO_2 insufflation are similar to the response in human patients (Duerr et al., 2008). As a result, acetazolamide may reduce postoperative pain in dogs having laparoscopic surgery with CO_2 insufflation.

Therefore, this study aimed to assess the effect of acetazolamide in postoperative pain after laparoscopic ovariectomy in dogs and compare those results with the traditional celiotomy ovariectomy. We hypothesised that variables associated with postsurgical pain/stress – serum and salivary cortisol – and pain scores from the University of Melbourne Pain Scale (UMPS) (Firth & Haldane, 1999) would be lower for the animals receiving perioperative acetazolamide and laparoscopy ovariectomy.

2 | MATERIALS AND METHODS

2.1 | Ethical considerations

The study protocol has been approved by the Ethical Committee of the Faculty of Medicine of the University of Lisbon. The procedures were performed under the Portuguese Government for Animal Care Guidelines (DL No 260/2012). A consent document advising of the risks of each procedure, especially for laparoscopic ovariectomy and the possible need to convert to an open celiotomy for situations such as uncontrollable haemorrhage or iatrogenic injury, was signed by the dog's owners.

2.2 | Study populations

A randomised parallel-group study design was conducted. Thirty healthy adult queens from different breeds, weighing between 4.8 and 31.4 kg, with ages between 4 months and 8 years old, were used in the study. Inclusion criteria included dogs with ideal body condition scores (Freeman et al., 2011), appropriate behaviour b, and not taking any drug. Dogs were deemed healthy based on clinical history, complete physical examination, and complete blood work (complete blood counts – CBC – and serum biochemistry parameters) on admission ($t = -1$ h). Presurgical blood biochemistry included glucose, fibrinogen, C-reactive protein, serum cortisol, and salivary cortisol. Animals' physical status was classified using the American Society of Anesthesiologists Classification (ASA) (Portier & Ida, 2018).

G* Power for Windows V. 3.1.6 was used to calculate sample size (Heinrich Heine Universität, Düsseldorf, Germany) (Faul et al., 2007; Erdfelder et al., 2009). The power analysis indicated that the number of animals included in the present study would allow detecting 1.0-point differences between groups for the Simple Descriptive Scale (SDS) and 3.0-point differences between groups for Numeric Rating Scale (NRS) scores with a power of 80% at 5% of the significance level.

A total of 32 dogs were assessed for eligibility. At enrolment, we excluded one dog for abnormalities in the blood analysis and another dog due to aggressive behaviour. Animals were randomly and blindly assigned to one of three groups of ten animals each: ventral median celiotomy ovariectomy (OVE group), laparoscopic ovariectomy (OVEL

group) and laparoscopic ovariectomy with acetazolamide administration (OVELA group). Food was withheld for 12 h before surgery. Also, water was withheld for 8 h before the procedure. On the day of the procedure, the animals were admitted.

The OVE group was composed of one Border Collie and nine mixed-breed dogs. The OVEL group comprised one Pitbull, one Yorkshire Terrier and eight mixed-breed dogs. Finally, the OVELA group consisted of one Miniature Poodle, one Golden Retriever, one Husky, and seven mixed-breed dogs.

2.3 | Anaesthesia

Before each surgery, a 25-mm, 22-gauge catheter (Introcan-W; B. Braun) was inserted into the cephalic vein for blood sample collection and drug administration. Venus peripheral blood (2.6 mL per animal) and the collection of salivary samples were collected 1 h ($t = -1$ h) prior to induction of the anaesthesia to obtain baseline values. In the OVELA group, 2 h before to induction, 25 mg/kg of acetazolamide in tablets at a dose of was administered orally.

For all the three groups, the identical anaesthesia protocol was used. The animals were premedicated with acepromazine (Calmivet; Vetoquinol) 0.05 mg/kg and tramadol (Tramadol; Labesfal) 5 mg/kg iv. Anaesthesia was induced with 4 mg/kg intravenous propofol (Propofol Lipuro; B. Braun) to allow dogs intubation and maintained with isoflurane (Vetflurane; Virbac) in 100% oxygen (100% Medicinal Oxigen; Conoxia). A semiclosed circuit was used. Before surgery, a dose of fentanyl (Fentanilo, Sandoz) 5 mcg/kg was added intravenously and then a constant rate infusion of 5 mcg/kg/h was started. During the anaesthesia, we used mechanical ventilation to improve intraoperative gas exchange. Dogs were properly clipped and moved to the surgical room, placed in dorsal recumbency, disinfected and draped for surgery. NaCl 0.9 % solution (B. Braun) was infused during surgery and recovery period (5 mL/kg/h) (Davis et al., 2013). At the moment of the induction, 8.75 mg/kg (7.0 mg amoxicillin, 1.75 mg clavulanic acid) (Synulox; Zoetis) was administered. The same antibiotic was prescribed for 7 days. A General Electric Anaesthesia equipment (Datex-Ohmeda 9100c NXT) was used with a semiclosed circuit with ventilation rate of 1 L per minute (0.5 L of oxygen and 0.5 L of air) and a tidal volume of 5–15 mL/kg. The anaesthetic machine incorporated the ventilator and animals were continuously monitored. Pulse oximetry, oscillometric noninvasive blood pressure, spirometry, electrocardiogram, capnography, oesophageal temperature, and an end-tidal fraction of anaesthetic gases was continuously monitored using a multiparameter monitor (B125 General Electric Medical Systems Information Technologies GmbH, Freiburg, Germany).

2.4 | Surgical procedures

2.4.1 | Ovariectomy

The open surgery was performed using the classic technique (Williams, 2013).

2.4.2 | Laparoscopic ovariectomy

Animals were positioned in dorsal recumbency. The urine bladder was emptied by catheterisation. For abdominal access, the pneumoperitoneum was established with a Veress needle (2.1 mm; Richard Wolf) inserted caudally into the xiphoid process. The CO_2 was provided via an automatic insufflator (Electronic Insufflator 2002; Cabot Medical) with a gas flow of 9 L/min to a pressure set at 9–11 mmHg. The first cannula (threaded, 5.5 mm in all cases) was placed 2 cm caudal to the umbilicus. We made a perimeter mark with the cannula to achieve the incision length through the skin and linea alba incision. The laparoscope (5.3 mm; 0°; Panoview) was inserted to evaluate the abdomen using standard clockwise rotation to avoid possible iatrogenic injuries.

Additionally, two cannulas were placed, each 3 cm cranial and caudal, to the first cannula, under direct vision of the laparoscope. The animal was rotated manually by an assistant into right lateral recumbency for identification of the left ovary. In all cases, forceps (5 mm; Robi; Karl Storz) was used to grasp, expose the ovary and suspend it to allow its removal. With high-frequency bipolar forceps (5 mm, RobiPlus; Karl Storz), the ovariectomy was completed by cauterising and transecting the proper ovarian ligament at the level of the uterine horn then the mesovarium and the suspensory ligament. The resected ovary was grasped by the proper ligament, elevated, and tacked to the body wall by passing a 40 mm, ½ circle curved cutting needle and sutured percutaneously through the body wall. The dog was manually positioned in left lateral recumbency to expose the right ovary. The ovariectomy was performed using the same technique described, except for the ovary not being tacked into the abdominal wall. The right ovary was grasped and secured with forceps. The dog was tilted into the right lateral recumbency, then the cannula with the forceps was pulled out, the 1-cm incision was extended to 1.5 cm, and the right ovary was removed from the abdomen. The pneumoperitoneum was partially lost, the cannula was inserted again, a clamp helped close the incision, and the pneumoperitoneum was reestablished. The left ovary was removed. The dog was turned into dorsal recumbency to inspect the abdominal cavity to evaluate for the presence of bleeding. Ovaries were checked to ensure complete excision; the two portals were removed, and the pneumoperitoneum was released. Abdominal incisions were closed in three layers: the first layer was muscular with the abdominal fascia and the second was the subcutaneous layer. A 2/0 absorbable synthetic monofilament glyconate suture (Monosyn; Braun) was used for suturing and a simple interrupted suture pattern was completed. A single absorbable 3-0 suture (Monosyn; Braun) was used for suturing the skin.

Once finalised the surgical procedure, dogs in all groups received one dosage of meloxicam 0.2 mg/kg SC (Metacam; Boehringer Ingelheim) (Hernández-Avalos et al., 2020; Cicirelli et al., 2021). Meloxicam was administered the following 2 days (0.1 mg/kg SC). All the dogs were bright, alert and responsive and were discharged home 2 days after surgery. One week after surgery, the animals returned to the veterinary hospital for a physical examination, evaluation of proper wound healing and collection of blood samples for a blood count (2.6 mL per animal).

2.5 | Recorded variables and assessment of postoperative pain

Breed, age, body weight, length of surgery and occurrence of intraoperative haemorrhage or surgical complications were among the data collected. Physiological data and behavioural response variables included in the UPMS were assessed preoperatively (baseline) and 1, 12 and 24 h after surgery to monitor the presence and severity of pain (Firth & Haldane, 1999). The UMPS score varies between 0 and 27 (Shields, 2009). In order to reduce the variability of this parameter, only one person who was familiar with the pain scoring system and was not aware of the procedure's group assignment evaluated the patient's level of pain. If the patient's pain level was higher than 10, rescue analgesia was justified, and methadone (0.5 mg/kg) was given as necessary (Cicirelli et al., 2021). Immediately after extubating ($t = 0$ h), blood samples (1.3 mL per animal) for measuring serum biochemistry parameters (glucose, cortisol, C-reactive protein and fibrinogen) and salivary cortisol and were collected at 1, 12 and 24 h. Blood was collected directly from the catheter placed in the cephalic vein at $t = -1$ h, $t = 0$ h and $t = 24$ h. CBC was measured 24 h (1.3 mL per animal) and 7 days (2.6 mL per animal) after surgery. C-reactive protein and fibrinogen were also measured 7 days after surgery.

Thus, the total of blood required from each animal was 7.8 mL (2.6 mL, $t = -1$ h), (1.3 mL, $t = 0$ h), (1.3 mL, $t = 24$ h) and (2.6 mL, $t = 7$ days), with an estimate of a maximum of 2.2 mL discarded per animal for the entire blood sampling process. CBC was analysed immediately after blood collection, and sera were stored at −18°C until the day of evaluation.

2.6 | Expression of the results and statistical analysis

Data with the normal distribution obtained from the study were expressed as means ± standard deviation (SD). For this purpose, the Kolmogorov-Smirnov test was used. Data obtained with nonnormal distribution or with high standard deviations were expressed as median because is a more appropriate average and absolute range (min and max) as an indicator of dispersion. Student *t*-tests to compare the differences in the mean values between groups were used. The interdependence of the variables was determined using Pearson's correlation coefficient. Parametric and nonparametric tests were conducted using Student's, Kruskal–Wallis and Friedman tests for intergroup and intragroup comparisons, respectively. Statistical analyses were performed using SPSS v.27.0 (SPSS Inc. Chicago IL). Significance was set as $p < 0.05$ for rejecting the null hypothesis.

3 | RESULTS

Previous studies used similar size groups for the sedation assessment and laparoscopic procedures (Van Goethem et al., 2003; Van Nimwegen et al., 2005; Wenkel et al., 2005; Mouton et al., 1999; Monteiro et al., 2016). All the animals included in the present study were classified in ASA 1 category (Portier & Ida, 2018). The animal caretakers gave their consent to participate in this survey, including the surgical procedures and blood sample collection.

TABLE 1 UMPS scores median (min and max) of dogs that underwent ovariectomy (OVE), laparoscopic ovariectomy (OVEL) and laparoscopic ovariectomy + acetazolamide (OVELA).

	Time after extubation		
Group	1 h	12 h	24 h
OVE	5.5 (1–10)	4.5 (1–8)	4.0 (2–8)
OVEL	1.0 (0–3)	1.0 (0–2)	1.0 (0–1)
OVELA	1.0 (0–3)	0.0 (0–2)	0.0 (0–0)

Animals included in the OVE group weighed (kg) between 8.1 and 22.7 (mean = 15.4); those included in the OVEL group weighed between 4.8 and 31.4 (mean = 15.9); and those included in the OVELA group weighed between 5.0 and 23.0 (mean = 12.2). There were no significant differences in the mean weight among the three groups.

Animals included in the OVE group were between 4 months and 6 years of age (mean = 1.62); those included in the OVEL group were between 4 months and 8 years of age (mean = 1.82); and those included in the OVELA group were between 5 months and 3 years of age (mean = 1.23). No significant age differences were observed between the OVEL and OVELA groups.

However, the average surgical time (in minutes) was significantly longer for laparoscopic procedures in the OVEL group (mean = 102.6; min 60; max 108.0; $p = 0.001$) and in the OVELA group (mean = 99.6; min = 75; max = 120; $p = 0.003$) compared to the OVE group (mean = 72.6; min = 60; max = 84). No significant differences were observed in the duration of surgery between the OVEL and OVELA groups.

Intraabdominal bleeding was not documented in OVEL and OVELA groups and was minimal and self-limited in the OVE group. No significant intraabdominal bleeding occurred in the laparoscopic procedures. Moreover, neither the OVE nor OVELA groups had any surgical complications. Therefore, conversion to an open surgery was not required for any of the animals included in the OVEL and OVELA groups. No side effects potentially attributable to acetazolamide were observed in the OVELA group.

3.1 | UMPS scores

All dogs had UMPS scores of 0 preoperatively. None of the animals in either group had a pain score requiring additional postoperative analgesia (i.e., >10 of a possible 27) after surgery. The OVELA group had the lowest pain scores at all postoperative time intervals. UMPS scores were statistically significantly lower in the OVEL group compared to the OVE group at 1 h after surgery ($p = 0.024$), 12 h ($p = 0.011$) and 24 h ($p = 0.04$). Also, UMPS scores were statistically lower in the OVELA group compared to the OVE group at 1 h ($p = 0.009$), 12 h ($p = 0.001$) and 24 h ($p = 0.002$). Then, animals undergoing open surgery (OVE group) had significantly higher pain scores at all time points after surgery compared to the OVEL and OVELA groups (Table 1).

TABLE 2 Median and range of serum cortisol levels (nmol/L); in each of the study groups measured throughout the duration of the study.

	Time after extubation			
Group	0 h*	1 h	12 h	24 h
OVE	117.1 (37.8–216.0)	382.5 (219.0–629.0)	106.5 (30.6–272.0)	90.9 (37.8–234.0)
OVEL	60.7 (29.0–167.0)	477.0 (144.0–590.0)	61.0 (19.5–222.0)	62.600 (20.3–129.0)
OVELA	55.9 (32.3–133.0)	457.0 (123.0–806.0)	90.5 (35.0–259.0)	74.0 (30.6–208.0)

*No statistical differences were found between groups at any time point in all the three groups.

TABLE 3 Median and range of salivary cortisol levels (nmol/L); in each of the study groups measured throughout the duration of the study.

		Time after extubation		
Group	0 h	1 h	12 h	24 h
OVE	6.1 (1.3–24.9)	27.6 (1.5–45.5)*	3.6 (1.8–18)	3.9 (1.9–12.3)
OVEL	4.8 (3.1–17.2)	61.9 (22.9–86.4)*	7.0 (4.1–11.3)	5.2 (2.9–11.1)
OVELA	6.1 (3.5–12.3)	36.2 (5.8–93.7)	7.6 (3.5–15.2)	5.2 (2.4–15.6)

*Statistical differences were found between OVE and OVEL group at 1 h time point ($p = 0.007$).

However, our results on UMPS scores did not show any statistical differences when the OVELA group was compared to the OVEL group at 1 h after surgery ($p = 0.515$), 12 h ($p = 0.375$) and 24 h ($p = 0.242$).

3.2 | Serum and salivary cortisol

All three groups' preoperative serum cortisol levels were within the standard range of 20–250 mmol/L. There were no statistically significant differences between groups preoperatively. Mean serum cortisol concentration peaked 1 h after surgery, began a trend towards the baseline and only returned to baseline 12 h after surgery. We found statistical differences between 1 h and the rest of the hours ($p = 0.0001$) in all three groups. Median serum cortisol concentrations for the OVE group for each time interval ranged from 90.9 nmol/L to 382.5 nmol/L; from 60.7 nmol/L to 477.0 nmol/L for the OVEL group; and from 55.9 nmol/L to 457.0 nmol/L for the OVELA group.

Related to cortisol concentrations shown in Table 2, we did not find statistical differences between the groups ($t = 0$ h, $p = 0.340$; $t = 1$ h, $p = 0.303$; $t = 12$ h, $p = 0.146$; $t = 24$ h, $p = 0.651$).

Median preoperative salivary cortisol concentrations were not statistically significantly different between groups (Table 3). Like serum cortisol results, mean salivary cortisol concentration peaked 1 h after surgery and returned to baseline 12 h after surgery, following the mean plasma cortisol fluctuation trend at intervals. A strong positive connection between serum and salivary cortisol levels was discovered ($r = 0.792$; $p = 0.01$). The median salivary cortisol concentration was significantly higher in the OVEL group (61.9 ng/mL) compared to the OVE group (27.6 ng/mL) 1 h after surgery ($p = 0.007$). On the other hand, the median salivary cortisol concentration in the OVELA group (36.2 ng/mL) was not significantly lower ($p = 0.075$) compared to the OVEL group (61.9 ng/mL). At any other time, no more significant differences between the groups were discovered (0, 12 or 24 h).

3.3 | Complete blood work

Samples were acquired at baseline, at 24 h and 7 days following extubation. White blood cell concentrations increased from baseline value in all the groups at 24 h. These differences were not statistically significant between groups ($t = 0$ h, $p = 0.087$; $t = 24$ h, $p = 0.139$; $t = 7$ days, $p = 0.659$).

No abnormal variation was observed in other parameters included in the complete blood work. Results of the red blood cell (RBC) counts and serum biochemistry parameters (glucose, C-reactive protein and fibrinogen) studied at all the time points in all three groups were within the reference range.

4 | DISCUSSION

4.1 | UMPS

For evaluating canine postoperative pain, the UMPS is considered a valid method (Firth & Haldane, 1999; Reid et al., 2018; Farokhzad et al., 2021; Okur & Polat, 2021; Costa et al., 2019). Six categories of multiple descriptors make up UMPS, including behavioural and physiological responses. By weighing particular behaviours, some observer bias can be removed (Mich & Hellyer, 2009). We chose this scale as previous studies showed its utility in laparoscopic postoperative pain assessment (Hancock et al., 2005; Freeman et al., 2009; Brad Case et al., 2011; Devitt et al., 2005; Haraguchi et al., 2017).

Using a variety of methods for pain assessment in veterinary medicine is considered the greatest method to prevent the unbalanced weighing of a single subjective or objective measurement (Mich & Hellyer, 2009; Mathews, 2000). Nonetheless, a gold standard has not been approved for measuring pain in veterinary patients (Hancock et al., 2005).

Objective measures such as clinical parameters (e.g. heart rate, respiratory rate and temperature) or biochemical test results (e.g. cortisol) are often used as indirect measures of pain. If they are not employed in conjunction with a concurrent assessment of behavioural changes, these metrics could result in inconsistent pain assessments (Hansen et al., 1997; Fox et al., 1998; Smith et al., 1996; Smith et al., 1999; Conzemius et al., 1997).

It was intended to cause the dogs as little discomfort as possible by restricting the amount of time points for blood and saliva sampling and measuring pain levels and, consequently, limiting potential interference in the studied variables motivated by stress/pain. Recent studies have used similar intervals for pain assessment (Hu et al., 2021; Hou et al., 2019).

Unlike other studies in which the pain relief duration lasted for a limited time of 6 h (Woehlck et al., 2003; Bala et al., 2015), we observed lower pain scores in the OVELA group compared to the OVEL group 12 h after surgery. However, these differences were not statistically significant in our study. Some reports have described that patient position is a factor that may contribute to CO_2 elimination in minimally invasive surgery in humans (Eaton et al., 2009). Thus, the rotation of dogs during the procedure and the sternal or lateral recumbency in the postoperative period, which could facilitate the rapid displacement of the residual CO_2 in the abdomen and its elimination, should be confirmed. Nevertheless, further studies with more animals are required to confirm this hypothesis on dogs.

Although pain scores in the open surgery (OVE) group were significantly higher throughout compared with the OVEL and OVELA groups, none of the dogs in the OVE group again required additional pain medication. Our results suggest that the anaesthetic and analgesic protocols were appropriate for the procedures used. However, different anaesthesia and analgesia protocols for routine ovariohysterectomies have been published (Gates et al., 2020). Further research is needed to compare these protocols and improve the safety and efficacy of the most used protocols and, finally, determine whether there is potential to improve the level of patient comfort.

This study could not find that the preoperative oral administration of acetazolamide reduced postoperative pain after laparoscopic ovariectomy in dogs. Specifically, pain scores for dogs in which acetazolamide was administered were lower at all postoperative time points compared to OVE and OVEL groups, nevertheless, these differences were not statistically significant.

4.2 | Serum and salivary cortisol

Cortisol levels can be measured and used as an accurate objective indicator of pain in animals (Smith et al., 1996; Benson et al., 1991; Popilskis et al., 1993; Lin et al., 1993). Different studies on dogs and cats reported a significant increase in cortisol due to surgical stress (Fox et al., 1998; Smith et al., 1996; Smith et al., 1999).

Since blood samples were only collected at baseline, the effect of stress on cortisol levels at this time was observed. However, our results conclude that the blood collection procedure was not enough to produce changes in the baseline value for each dog since we did not identify significant differences at baseline within groups. These findings have also been reported in a previous study (Kobelt et al., 2003).

The variation of cortisol concentrations followed a similar path to salivary cortisol. Therefore, a high positive correlation ($r = 0.792$; $p = 0.001$) was found between serum and salivary cortisol concentrations. These results agree with previous studies on dogs (Vincent & Michell, 1992; Giannetto et al., 2014).

Due to the fact that noninvasive salivary cortisol sampling and serum cortisol in dogs have a strong correlation (Beerda et al., 1996), it has been increasingly used for measuring stress response in this species (Vincent & Michell, 1992; Beerda et al., 1996; Beerda et al., 1998).

According to other laparoscopic ovariohysterectomy studies in dogs (Devitt et al., 2005; Ko et al., 2000), 1 h following surgery, cortisol experienced its first and highest postoperative peak. Thus, the mean salivary cortisol concentration in the OVELA group was not significantly lower than in the OVEL group. The anaesthesia protocol was the same for each group, therefore, it appears that anaesthesia by itself would not explain the variation in saliva cortisol concentrations at 1-h after surgery (see Table 4). On the other hand, the similar salivary cortisol concentration at hour 1 in the OVELA and OVE groups did not reflect a lower stress response from the effect of acetazolamide.

TABLE 4 White blood cells concentrations ($\times 10^9$/L; mean ± SE) in the different groups at any time point studied.

	Time		
Group	0 h	24 h	7 d
OVE	11.32 ± 0.73	15.90 ± 1.03	14.05 ± 1.72
OVEL	13.95 ± 0.75	19.94 ± 1.25	13.63 ± 0.74
OVELA	13.74 ± 2.28	20.97 ± 2.68	14.79 ± 2.85

No significant differences were observed in any group from preoperative concentration.

4.3 | Complete blood count

Besides stress and pain, tissue damage from surgical procedures can stimulate, as soon as 12–36 h after surgery, the hypothalamus–hypophysis–adrenal axis to liberate glucocorticoids (cortisol), which increase the production and migration of neutrophils (Katz et al., 2012).

Laparoscopic surgery can prevent or reduce alterations such as leucocytosis (Katz et al., 2012). Our study showed an increase in WBC concentrations from baseline in all the groups 24 h after surgery; however, these differences were not statistically significant. One week

after surgery, the WBC concentrations returned to baseline. Thus, our findings corroborate previous results (Alves et al., 2010), suggesting that WBC concentrations may be helpful for the evaluation of inflammatory response induced by surgery.

4.4 | Acetazolamide

The duration of peritoneal CO_2 after laparoscopic surgery in people resolves within 6 h in most patients, leaving some people with small amounts of residual gas (Woehlck et al., 2003).

After a single dose of acetazolamide, peak effects occur within 2–4 h and last for 4–6 h in small animals (Plumb, 2011). Another report suggested that treatment of postoperative pain derived from CO_2 insufflation could be necessary 6 h after the procedure (Woehlck et al., 2003). This period coincided with the lasting time effect of acetazolamide (Plumb, 2011; Roberts, 1985). In light of these studies, a single dose of 25 mg/kg was administered in the OVELA group 2 h before anaesthesia induction, which corresponds to the maximal effects of acetazolamide in the dog. We decided on acetazolamide administration time based on pharmacokinetics (Plumb, 2011; Roberts, 1985). Then, administration 2 h before induction of anaesthesia allowed the peak effects of acetazolamide to be 2–4 h after its administration. Since we did not find differences between the groups in blood and salivary cortisol values at baseline, we assumed that oral administration of acetazolamide before sample collection did not interfere with these values, allowing adequate comparison of their variations postoperatively.

Although the specimens in the present study were of different breeds, they represented healthy dogs, which normally come to veterinary hospitals for elective neutering. We believe that the differences detected truly represent those observed between groups since there were no significant differences in mean group age and weight.

On the other hand, acetazolamide-induced metabolic acidosis, which reaches its maximum within 24 h in humans (Schmickl et al., 2021), could be a valuable issue. Overdose of acetazolamide (625 mg/kg) can produce severe hyperchloremic metabolic acidosis and hypokalaemia in dogs (Johnston et al., 2021). The animals included in this study received 25 mg/kg acetazolamide, and none of the animals developed any signs indicative of metabolic acidosis. Future studies should include programmed serial blood tests to monitor blood pH, arterial PCO_2 and PaO_2 to assess the relationship of these parameters to the effects of acetazolamide on acid–base status. In any case, adequate ventilation of animals during anaesthesia should always be monitored to avoid adverse side effects.

Several studies reported that laparoscopic procedures take longer than the traditional midline open technique (Culp et al., 2009; Davidson et al., 2004). In our study, the celiotomy (OVE) approach was the fastest, and surgical time was significantly longer for laparoscopic ovariectomy (OVEL and OVELA groups). We attributed the longer time of surgery to the recumbency changes produced in each laparoscopic procedure in both OVEL and OVEL groups. Using high-frequency bipolar electrocoagulation, we did not register any intraabdominal bleeding in the laparoscopic procedures.

5 | LIMITATIONS

This study showed limitations because the sample size was not as significant as other studies evaluating pain. However, it is essential to highlight that pet owners do not easily choose this procedure. Then, it is challenging to obtain groups with a large animal's number. On the other hand, the number of evaluation times could have been higher to give a more detailed evaluation of the evolution of the variables throughout the postoperative period. Further studies should be performed to identify electrolyte disturbances caused by acetazolamide diuretic effects and arterial blood gas alterations that CO_2 can induce.

6 | CONCLUSIONS

Although the results of the present study do not demonstrate statistically significant differences between the groups studied, there is evidence that a benefit of preoperative administration of acetazolamide may exist for the management of postoperative pain in dogs after laparoscopic surgeries. Then, we suggest that further studies with a larger number of animals are required to demonstrate that acetazolamide could be considered helpful as an adjuvant in a multimodal postoperative analgesia protocol for laparoscopic ovariectomy in dogs.

AUTHOR CONTRIBUTIONS

Conceptualisation: I.T.T., R.R., J.P.S.L., C.G.V. and S.D.C. Methodology: I.T.T., R.R., J.P.S.L., C.G.V. and S.D.C. Software: J.A.C. Validation: I.T.T., R.R., J.P.S.L., C.G.V., S.D.C., J.A.C. and J.R.J. Formal analysis: I.T.T., R.R., J.P.S.L., C.G.V., S.D.C., J.A.C. and J.R.J. Investigation: I.T.T., R.R., J.P.S.L., C.G.V., S.D.C., J.A.C. and J.R.J. Resources: I.T.T., R.R., J.P.S.L., C.G.V. and S.D.C. Data curation: I.T.T. and J.A.C. Writing – original draft preparation: I.T.T., R.R., J.P.S.L., C.G.V., S.D.C., J.A.C. and J.R.J. Writing – review and editing: I.T.T., J.A.C. and J.R.J. Visualisation: I.T.T., R.R., J.P.S.L., C.G.V., S.D.C., J.A.C. and J.R.J. Supervision: I.T.T., R.R., J.P.S.L., C.G.V., S.D.C., J.A.C. and J.R.J. Project administration: I.T.T., R.R., J.P.S.L., C.G.V. and S.D.C. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study protocol has been approved by the Faculty of Veterinary Medicine's Ethical Committee at the University of Lisbon. The procedure was carried out following the Portuguese Governmentt's Guidelines for Animal Care (Decreto-Lei N° 260/2012).

PEER REVIEW

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