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Research article

Hematological and biochemical variations in dogs with osteoarticular pain undergoing treatment with meloxicam and cannabidiol

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Abstract

Osteoarticular diseases in dogs are a significant source of chronic pain, adversely affecting their quality of life. Traditional treatment often relies on nonsteroidal anti-inflammatory drugs (NSAIDs), which can lead to undesirable side effects. Conversely, cannabidiol (CBD) is increasingly being explored for managing osteoarticular pain across various animal species. However, there is limited research on the effects of these pharmacological compounds on the hematological and biochemical profiles of dogs with osteoarthritis. This study aimed to assess the hematological and biochemical variations in dogs experiencing osteoarticular pain while receiving therapeutic doses of meloxicam (MELX) and increasing doses of CBD over 8 weeks. A total of 16 dogs with osteoarticular pain were divided into two groups: MELX and CBD. The MELX group received meloxicam (0.2 mg/kg on day one, followed by 0.1 mg/kg daily thereafter), and the CBD group was administered 2 percent CBD cannabis oil, starting at 0.5 mg/5 kg in the first week and increasing by 0.5 mg/5 kg each subsequent week. Hematological and biochemical analyses were conducted on days 0 (baseline) and 57 (one day post-treatment). Significant changes were noted in erythrocyte counts, monocytes, lymphocytes, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), leukocytes, and eosinophils in the MELX group. In contrast, the CBD group exhibited significant changes only in MCV and leukocyte counts. Additionally, the MELX group showed alterations in alkaline phosphatase (ALP), urea, and creatinine levels, whereas the CBD group demonstrated a notable decrease in urea and ALP. Overall, the administration of increasing doses of CBD resulted in minimal changes to hematological parameters and did not indicate renal or hepatic toxicity, suggesting that CBD may serve as a viable alternative treatment for osteoarticular diseases in dogs.

Keywords: Cannabis, Chronic pain, NSAIDs, Osteoarthritis, Osteopathology, Toxicity

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Introduction

Osteoarticular diseases in dogs are commonly encountered in veterinary practice, with the primary goal of alleviating pain and enhancing the animal's quality of life (Epstein et al., 2015). Veterinary professionals often prescribe nonsteroidal anti-inflammatory drugs (NSAIDs) for this purpose. However, the prolonged use of these medications can lead to adverse effects, including gastric irritation, hepatotoxicity, and nephrotoxicity, which can limit their utility in

treating osteoarticular pain (Chalifoux et al., 2023).

Meloxicam is frequently highlighted in the literature for its efficacy in managing osteoarthritis in dogs, generally exhibiting minimal and transient side effects (Sandersoln et al., 2009). Nonetheless, some studies indicate potential negative impacts on the hematological profile, particularly when administered over short durations (Smith et al., 2020). In recent years, cannabidiol (CBD), a non-psychoactive component of cannabis (*Cannabis sativa*), has gained attention for its analgesic properties (ElSohly et al., 2017). Its application in managing osteoarticular pain and neurodegenerative diseases has become increasingly prominent (Mlost et al., 2020; Verrico et al., 2020) in both human and veterinary medicine, with reports suggesting minimal side effects, typically mild and transient when they occur (Vaughn et al., 2021).

Hematological and biochemical tests offer valuable insights into the overall health status of animals. Despite this, there is a paucity of information regarding the hematological and biochemical changes associated with the prolonged use of meloxicam or CBD in dogs with osteoarticular pain. This lack of data raises important questions about the safety and appropriate dosing of CBD. Therefore, the objective of the present study was to evaluate the hematological and biochemical variations in dogs suffering from osteoarticular pain while receiving therapeutic doses of meloxicam and escalating doses of CBD over 8 weeks.

Material and methods

Ethical approval

This research was approved by the Animal Research Bioethics Committee of the Veterinary Medicine and Animal Husbandry program at the Faculty of Agricultural Sciences, Antenor Orrego Private University (UPAO), under Resolution No. 0483-2021-FCA-UPAO. Informed consent was obtained from the owners of the animals participating in the study. They were fully briefed on the study's objectives and methodology, ensuring compliance with the international guidelines set forth by Directive 2010/63/EU regarding protecting animals used for scientific purposes. Protocols were established for the immediate withdrawal of any animal exhibiting signs of poisoning or adverse reactions to the administered drugs during the research.

Study area and period

This quantitative, experimental, single-blind study was conducted in Trujillo (8°6'57.6" S, 79°1'47.9" W), located in the La Libertad Region of northern Peru, from December 2021 to March 2022. The city experiences minimum and maximum temperatures of 18°C and 34°C, respectively, with an average relative humidity of 76 percent.

Selection of animals and experimental groups

Dogs were selected from various veterinary clinics in Trujillo, regardless of their breed or sex, as long as they had no infectious diseases, neoplasia, or pharmacological treatments in the three months before the study. All selected animals exhibited osteoarticular pain, which was diagnosed by a specialist through clinical and radiological examinations. Before starting the research, all dogs underwent biochemical and hematological analyses to rule out renal, hepatic, or other underlying conditions. Animals with laboratory results outside normal parameters were excluded from the study, as well as puppies and pregnant females. Ultimately, 16 dogs aged between 4 and 10 years, weighing between 11 and 20 kg, met the inclusion criteria and were fed a diet of 100 percent commercial food with ad libitum access to water.

The dogs were randomly assigned to two groups: the MELX group and the CBD group, each consisting of 8 animals. The MELX group received standard analgesic treatment for osteoarticular pain with oral meloxicam, starting at a dose of 0.2 mg/kg on the first day, followed by 0.1 mg/kg daily for 8 weeks (Gonzáles-Corrales et al., 2020). The CBD group received 2 percent cannabis oil (200 mg/10 mL) containing cannabidiol (CBD) orally. The initial dose of CBD was 0.5 mg/5 kg of body weight in the first week, increasing by 0.5 mg/5kg each subsequent week, reaching a final dose of 4 mg/5 kg by the eighth week. Both treatments were administered once daily after meals to minimize the risk of gastric lesions, particularly with meloxicam (Elfadadny et al., 2021). Administration was carried out by a specialist veterinarian at the owner's home, ensuring the owner remained unaware of which treatment their pet was receiving.

Hematological and biochemical profile

In both study groups, we assessed a range of hematological parameters, including red blood cell count (10^6/µL), hematocrit (%), hemoglobin (g/dL), mean corpuscular volume (MCV [fL]), mean corpuscular hemoglobin (MCH [pg]), and mean corpuscular hemoglobin concentration (MCHC [g/dL]). We also measured leukocyte count (/µL), platelet count (10^9/L), segmented neutrophils (/µL), band neutrophils (/µL), eosinophils (/µL), monocytes (/µL), and lymphocytes (/µL). For the biochemical analysis, we determined levels of alanine aminotransferase (ALT [U/L]), alkaline phosphatase (ALP [U/L]), urea (mg/dL), and creatinine (mg/dL).

Blood samples were collected at two-time points: day 0 (one day before the start of the study) and day 57 (one day after the study's conclusion), using sterile vacuum tubes for venipuncture. The hematological profile was analyzed using an automated hematology analyzer (Mindray, China, model BC-30 Vet), while biochemical analyses were conducted using the Catalyst One analyzer from IDEXX (IDEXX, Westbrook, USA).

Statistical analysis

Data were first subjected to the Shapiro-Wilk normality test to assess their distribution. To evaluate differences in hematological and biochemical profiles before and after treatment, we employed the Student's parametric t-test for related samples, utilizing GraphPad Prism v. 10.2.3 software. A significance level of $p<0.05$ was established for all analyses.

Results

Throughout the study, only one dog in the MELX group experienced vomiting, which resolved quickly without the need for additional medication. All animals remained within the established hematological and biochemical parameters for their species. However, both study groups observed notable variations in certain hematological and biochemical indices.

Hematological parameters in dogs treated with meloxicam

Significant variations ($p<0.05$) were noted in the number of erythrocytes, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), leukocytes, eosinophils, monocytes, and lymphocytes. In contrast, no significant changes were detected in hemoglobin levels, mean corpuscular hemoglobin concentration (MCHC), platelet count, band neutrophils, or segmented neutrophils ($p>0.05$) by the end of the study (Figure 1).

As illustrated in Figure 1, there was a significant increase in the mean number of erythrocytes ($p<0.01$), rising from 6.46×10^6/µL to 6.86×10^6/µL by day 57. Increases were also observed in monocytes (from 262/µL to 309.1/µL) and lymphocytes (from 2237/µL to 2759.5/µL). Conversely, significant decreases ($p<0.05$) were recorded at the conclusion of the study in hematocrit (from 46.6% to 44.2%), MCV (from 66.3 fL to 64.1 fL), MCH (from 23.3 pg to 21.7 pg), leukocyte count (from 11,784/µL to 10,548.2/µL), and eosinophils (from 375.2/µL to 310.8/µL).

Hematological parameters in dogs treated with CBD

As shown in Figure 2, significant changes ($p< 0.05$) were only observed in the mean values of mean corpuscular volume (MCV), which decreased from 70.8 fL to 65.7 fL, and leukocyte count, which decreased from 11,850.3/µL to 11,061.5/µL ($p<0.05$) by day 57.

In contrast, other parameters did not exhibit significant changes: erythrocyte count increased slightly from 6.86×10^6/µL to 6.92×10^6/µL; hematocrit decreased from 45.1% to 44.09%; hemoglobin levels fell from 15.6 g/dL to 14.61 g/dL; mean corpuscular hemoglobin (MCH) decreased from 23 pg to 21.5 pg; and mean corpuscular hemoglobin concentration (MCHC) decreased from 34.5 g/dL to 33.5 g/dL. Additionally, platelet counts remained unchanged at 193.3×10^9/L, while segmented neutrophils decreased from 9,399.5/µL to 9,152.9/µL, band neutrophils from 155.1/µL to 144.8/µL, eosinophils from 376.1/µL to 365.3/µL, monocytes from 313.9/µL to 317.9/µL, and lymphocytes (from 2,307.1/µL to 2,634.6/µL) did not show significant changes on their levels ($p>0.05$).

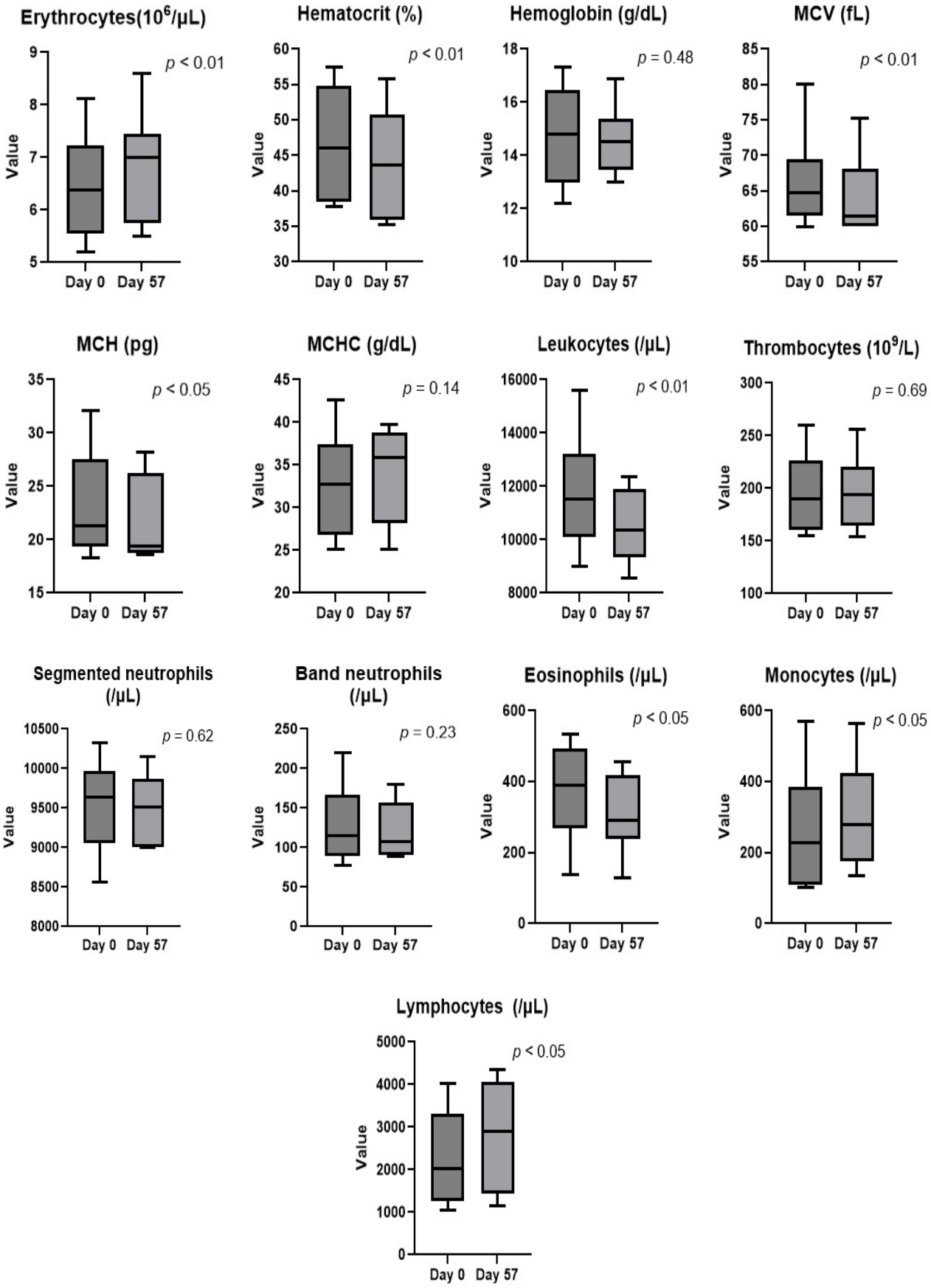

Figure 1: Box-and-whisker plot of hematological values in dogs treated with meloxicam (0.2 mg/kg on day 1, followed by 0.1 mg/kg thereafter) on days 0 and 57. The significance levels from the Student's t-test for related samples are indicated for each parameter (p<0.05) (n=8).

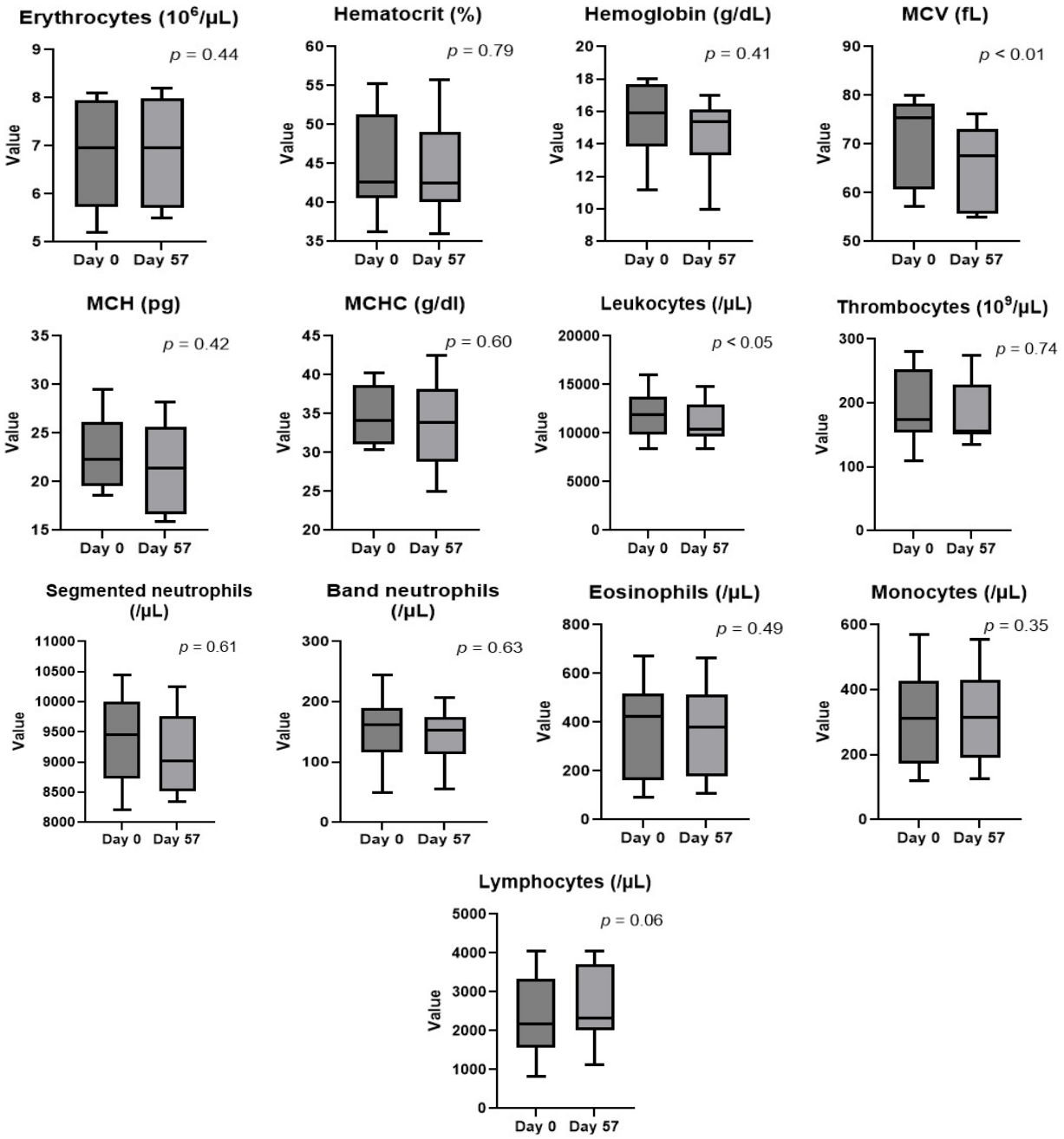

Figure 2: Box-and-whisker plot of hematologic values in dogs undergoing increasing CBD treatment (an increase of 0.5 mg/5 kg/week) on days 0 and 57. The significance level of the Student's t-test for related samples is shown (p<0.05) (n=8).

Biochemical parameters in the CBD and MELX groups

The mean levels of ALP (from 75 U/L on day 0 to 71.3 U/L on day 57) and urea (from 39.6 mg/dL to 35.4 mg/dL) decreased significantly (p<0.05) at the end of the study in dogs in the CBD group. ALP also decreased (p<0.05) (from 69.5 to 63.0 U/L) in the MELX group; the opposite occurred with urea (from 40.4 mg/dL to 43.5 mg/dL) and creatinine (from 1.0 mg/dL to 1.9 mg/dL). Some dogs exceeded the upper limit in the last parameter mentioned (Figure 3).

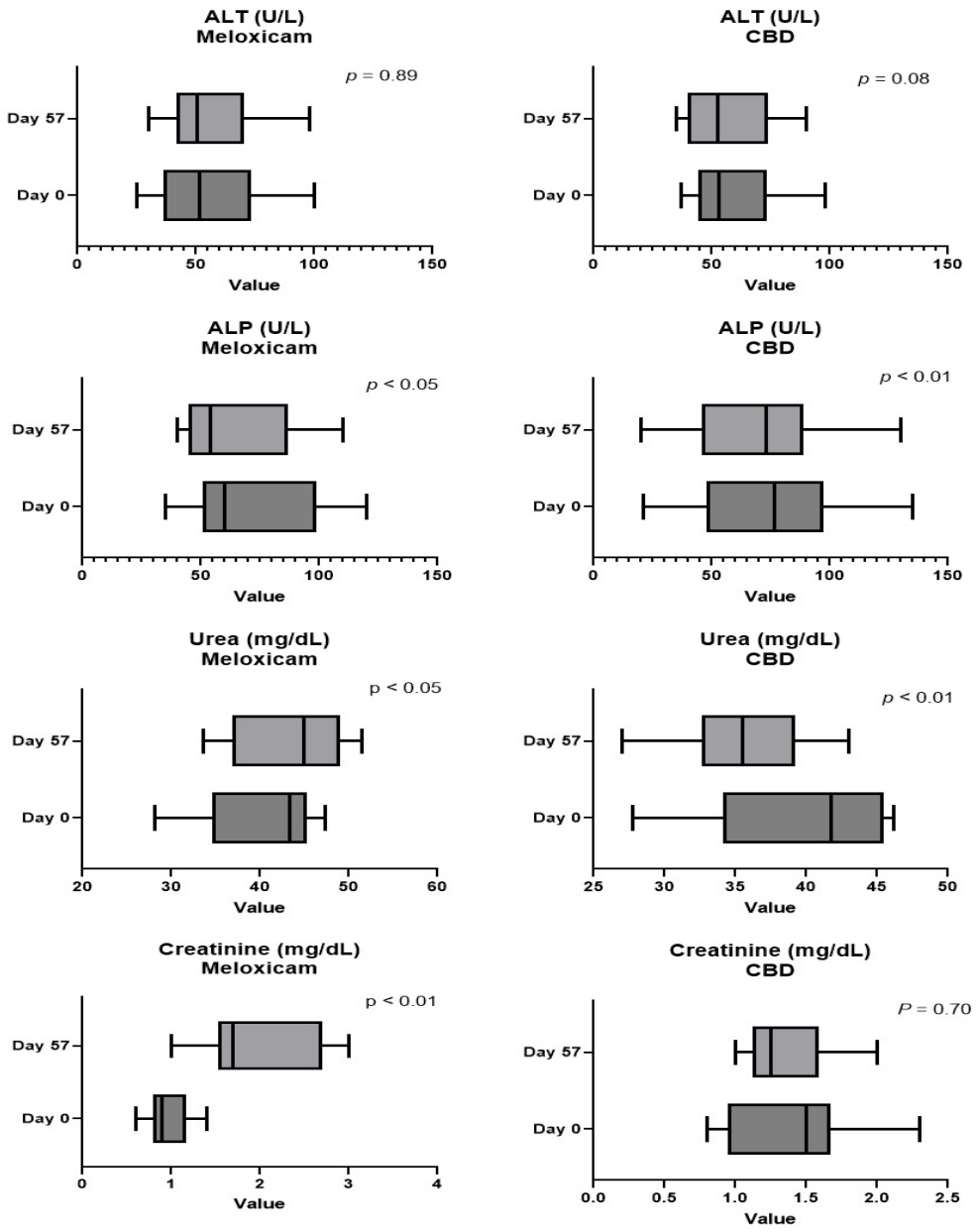

Figure 3: Box-and-whisker plot of the variations in ALT, ALP, creatinine, and urea levels on days 0 and 57 in dogs receiving therapeutic doses of meloxicam (0.2 mg/kg on day 1 and 0.1 mg/kg until the end of the study) and increasing doses of CBD (0.5 mg/5 kg/week) on days 0 and 57. The significance level of the Student's t-test for related samples is shown (p<0.05) (n=16).

Discussion

Hematological and biochemical analyses are essential tools in veterinary practice, enabling the evaluation of health status, establishment of diagnoses and prognoses, and assessment of treatment effects on animals (Yazlık et al., 2022). Both compounds in this study were administered orally, a route generally considered one of the safest—especially for CBD—compared to rectal or nasal administration (Polidoro et al., 2022). This approach facilitates the achievement of optimal blood levels. The results, however, indicate that the hematological parameters of the dogs in both the MELX and CBD groups remained within normal ranges. However, significant changes were noted in certain blood indices.

While thrombocytopenia was anticipated in the MELX group, as suggested by previous studies, it typically occurs with the administration of higher doses over prolonged periods (Zanuzzo et al., 2015) or in the presence of neoplasias and infectious diseases (Martín-Ambrosio-Francés et al., 2023). In contrast, thrombocytopenia usually does not manifest significantly in other species during short

treatment regimens (14 days) (Montesinos et al., 2015). Moreover, minimal changes in platelet counts were reported in dogs with osteoarthritis treated with meloxicam at doses of 0.05 mg or 0.1 mg/kg every 24 hours for 7 or 14 days (Brainard et al., 2007; Blois et al., 2010), suggesting that any minor variations in platelet levels are likely associated with therapeutic doses of meloxicam.

Similarly, variations were noted in the red blood cell count of the MELX group. These changes are less pronounced in animals treated with this drug for short durations (Lieser et al., 2021). In contrast, higher doses (0.2 mg/kg) can decrease erythrocyte levels, potentially due to the formation of gastric ulcers (Elfadadny et al., 2021). Unexpectedly, our study observed a significant increase in erythrocyte counts in the MELX group. This may be attributed to extrinsic factors, such as the hydration level of the animals at the time of sampling, particularly since the research was conducted during the summer months. Conversely, the dogs in the CBD group exhibited minimal variations in hematological results, with the exception of mean corpuscular volume (MCV) and leukocyte counts. Such minor fluctuations have also been reported in experimental studies involving CBD administration in healthy dogs and those with osteoarthritis, with no adverse symptoms, noted (Deabold et al., 2019; Gamble et al., 2018; Vaughn et al., 2020).

In both study groups, a decrease in ALP levels was observed by day 57. Meloxicam, as a selective Cyclooxygenase-2 (COX-2) inhibitor, exhibits an osteoprotective function and actively participates in osteogenesis in dogs with osteoarticular dysfunction, likely through a compensatory mechanism that restores the synthesis of Prostaglandin E2 (PGE2) (Oh et al., 2014). The decrease in ALP levels suggests that liver damage in the MELX group may be minimal, differing from the adverse effects associated with other nonsteroidal anti-inflammatory drugs, such as diclofenac and celecoxib (Sriuttha et al., 2018). However, meloxicam toxicity has been documented in vitro studies at higher doses (Burukoglu et al., 2016) and may be influenced by genetic factors, age, and sex (Leise et al., 2014). Future studies should evaluate these risk factors associated with meloxicam use in dogs, particularly in those with osteoarticular diseases. In the CBD group, changes in ALP levels also demonstrated significant variations; however, these alterations typically do not correlate with animal discomfort (McGrath et al., 2019).

Urea and creatinine levels increased significantly in the MELX group by day 57, though they remained below the upper limit of the normal range. In cats, renal function is not significantly affected by prolonged administration of Meloxicam at doses below 0.02 mg/kg (Gowan et al., 2011). Conversely, renal function can be compromised in sheep with a short-term administration of 1 mg/kg of meloxicam (Kongara et al., 2023). Similar to our findings, previous research indicates that meloxicam can lead to elevated creatinine levels, reflecting potential damage to renal functionality and histological structure (Inal et al., 2014).

Interestingly, the CBD group exhibited a significant decrease in urea levels by the end of the study. This finding aligns with experimental studies demonstrating that prolonged CBD administration is associated with reduced oxidative stress in the kidneys (Pan et al., 2009) and improved renal function through the activation of the cannabinoid receptor 2 (CB2), which plays a role in maintaining renal physiological homeostasis (Mukhopadhyay et al., 2010; Chua et al., 2019).

Additionally, the CBD group showed a significant decrease in ALP levels, attributed to the hepatoprotective effects of cannabidiol, which can help mitigate adverse outcomes such as liver fibrosis (Del Río et al., 2022). However, other studies have reported increased ALP levels in dogs receiving daily doses of 2 mg/kg twice a day or 12 mg/kg for 28 days (Gamble et al., 2018; Vaughn et al., 2021). This increase was also noted when the dosage was doubled quickly (Vaughn et al., 2020). These findings suggest that dogs may develop tolerance to escalating doses of CBD, which could explain the lack of significant biochemical profile changes observed (Chicoine et al., 2020). Notably, no neurological effects were evident in our study, even with the administration of a dose of 4 mg/5 kg in the final week.

At the end of the study, a significant improvement was observed in the dogs in the CBD group, characterized by the absence of pain in the osteoarthritis-affected areas and increased physical activity. This enhancement aligns with previous studies' findings, particularly in

osteoarticular inflammation cases. However, those studies employed a wide range of doses and application durations (Lima et al., 2022) compared to the structured protocol used in the present research.

Conclusions

The administration of increasing doses of CBD over 8 weeks resulted in minimal changes to hematological and biochemical parameters, indicating that this compound may be safe even at higher doses without adversely affecting the health of the animals, including those with kidney or liver impairments. In contrast, meloxicam, commonly used in veterinary practice to treat osteoarticular conditions and chronic pain, exhibits a more variable side effect profile. These findings warrant further research, incorporating new variables and a larger sample size. A significant challenge remains in pet owners' willingness to explore alternative therapies for chronic pain, alongside considerations of their availability for home treatment and the high cost of cannabidiol in Peru. Additionally, it is essential to establish pain indices and conduct complementary tests to evaluate inflammation levels or cartilage regeneration following prolonged CBD administration. Despite these advancements, there is still much to explore regarding the use of cannabidiol in dogs, particularly in specific conditions such as osteoarticular pain.

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Author Contributions. Y.C.S., R.R.R: conceptualization and study design. R.M.M., J.R.P.V: methodology and data analysis. R.R.R., J.R.P.V: writing of the manuscript, Y.C.S., R.R.R., R.M.M: reviewing and editing. All authors have reviewed and approved the final version of the document.

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