2024, Scienceline Publication
World's Veterinary Journal
World Vet J, 14(1): 15-25.
ISSN 2322-4568

DOI: https://dx.doi.org/10.54203/scil.2024.wvj3
PII: S232245682400003-14

Comparative Effects of Meloxicam and Phenylbutazone on Clinical Outcomes and Acute Phase Response in Sheep with Acute Respiratory Disease

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ORIGINAL ARTICLE
Received: January 03, 2024
Revised: February 19, 2024
Accepted: February 26, 2024
Published: March 25, 2024

ABSTRACT

The ovine respiratory complex (ORC) is one of the most common respiratory diseases observed in sheep. The objective of the present investigation was to evaluate the comparative therapeutic efficacy of two non-steroidal anti-inflammatory drugs (meloxicam and phenylbutazone) for the treatment of the ORC. For this purpose, 33 Ossimi sheep were randomly assigned into three treatment groups (11 each). Group 1 was treated with amoxicillin long-acting (LA) and meloxicam, group 2 received amoxicillin LA and phenylbutazone, and group 3 was treated with amoxicillin LA alone. Sheep were examined clinically and clinical index scores were recorded before and after treatment. Additionally, blood samples were collected from each sheep. After 14 days of treatment, sheep of group 1 indicated significant improvements in their clinical index scores and a reduction in total leukocyte count. However, there was a significant increase in red blood cell count, hemoglobin, and MCHC%. There was a significant decrease in the serum globulin, copper, and haptoglobin in group 1, compared to sheep of groups 2 and 3. Based on the results of this study, administering meloxicam to sheep with an ovine respiratory complex resulted in significant improvements in clinical outcomes and significant corrections in above mentioned hematological and biochemical parameters. Although phenylbutazone proved to be less effective, it still demonstrated some degree of efficacy in treating this condition. This study suggests that meloxicam may be a more effective treatment option for ORC with phenylbutazone.

Keywords: Acute phase protein, Amoxicillin, Anti-inflammatory, Ovine respiratory complex

INTRODUCTION

Ovine respiratory complex (ORC) is one of the main diseases affecting small ruminants in many countries (Tibbo et al., 2001; Navarro et al., 2019). It commonly affects individuals or groups of sheep and frequently requires a combination of infectious agents as well as managemental risk factors (Hindson and Winter, 2008). The ovine respiratory complex is a feedlot production health concern in sheep-rearing countries (González et al., 2016; Lacasta et al., 2019). The outcomes of ORC include increased mortality, reduced growth rate, waste in the slaughterhouse, medicine expenditures, and labor expenses related to treatment are the outcomes of ORC (Baghezza et al., 2021).

Sheep are more vulnerable to respiratory infections owing to the interactions between several viral and bacterial pathogens, impaired pulmonary defense mechanisms, and husbandry-related factors (Brogden et al., 1998). The bacteria most implicated in ORC are *Mannheimia haemolytica*, *Mycoplasma ovipneumoniae, Pasteurella multocida, Bibersteinia trehalosi*, *Trueperella pyogenes*, and *Escherichia coli* (Saura Armelles, 2017). A compromised immune system can lead to the invasion and growth of pathogenic bacteria in lung tissue, with subsequent inflammation and severe clinical signs (Mosier, 2014; Pahal et al., 2018; Franco et al., 2019).

Clinically, ORC can be acute or chronic (Kumar et al., 2014), where acute ORC in sheep is characterized by fever, depression, weight loss, mucopurulent discharge, increased respiratory rate, and crackles in the anterior thorax (Gilmour et al., 1983). In contrast, sheep affected by chronic ORC experience chronic soft cough and mucopurulent nasal discharge (Scott, 2015).

To cite this paper: Alwayel A., Marzok M, Gioushy M, Kandeel M, Almubarak A, Hamad Y, Shousha S, El-khodery S (2024). Comparative Effects of Meloxicam and Phenylbutazone on Clinical Outcomes and Acute Phase Response in Sheep with Acute Respiratory Disease. *World Vet. J.,* 14 (1): 15-25. DOI: https://dx.doi.org/10.54203/scil.2024.wvj3

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been used as a supplementary treatment alongside antimicrobial therapy to address ORC because they possess analgesic, antipyretic, and anti-inflammatory properties (Politis et al., 2019). Meloxicam is an oxicam-class NSAID with powerful anti-inflammatory, analgesic, and antipyretic effects (Xu et al., 2014). It operates by inhibiting cyclooxygenase-2 enzymes, which lessens the production of tumor necrosis factor, an inflammatory cytokine that is produced during respiratory tract infection (Bednarek et al., 2003; Hirsch et al., 2003; Curry et al., 2005). In cattle, meloxicam has been clinically evaluated widely as an adjunctive therapy for the treatment of respiratory tract diseases (Salamon et al., 2000; Schmidt et al., 2000). Similarly, Phenylbutazone is an effective NSAID with antipyretic and analgesic properties and has been used in veterinary medicine for more than five decades to treat musculoskeletal system inflammation, soft tissue inflammation, and laminitis (Flood and Stewart, 2022). While Phenylbutazone has been proven to be very effective in treating respiratory disease in calves owing to its potent anti-inflammatory effects, there is a paucity of information on its effectiveness as a supplementary therapy for treating ORC in sheep (El-Deeb et al., 2021).

The effect of anti-inflammatory drugs on acute phase proteins in calves with respiratory diseases has been presented (El-Deeb et al., 2021), and in sheep with pneumonic pasteurellosis (El-Deeb and Elmoslemany, 2016). However, there is little information about the effect of meloxicam on clinical and acute phase proteins (APPs) in sheep with ORC.

Therefore, the aim of the present study was to compare the therapeutic efficacy of meloxicam and phenylbutazone on the clinical outcomes, hematological parameters, and selected APPs in Ossimi sheep affected by ORC.

MATERIAL AND METHODS

Ethical approval

Ethical approval for this experiment was given by the committee of King Faisal University No. KFU-REC-2023-NoV-ETHICS-1371.

Animals and clinical examination

In this study, a total of 33 Ossimi sheep with ORC were examined. To diagnose ORC, a systemic clinical examination was conducted with signs of anorexia, depression, coughing, nasal discharge, and high body temperature (≥ 40°C; Lacasta et al., 2019). On the first examination and before treatment, clinical findings for each sheep were identified and scored, and the sum of such clinical index scores was recorded (Table 1). Sheep were randomly selected from different herds in Dakahlia and Qalubia governorates. The age of the sheep ranged from three months to two years (Mean 12 ± 55 months).

The body weight of examined sheep ranged from 4 to 40 kg (Mean 19 ±8.4 kg). Sheep were raised in smallholder flocks and kept indoors. Sheep were fed on green fooders and 250 gm concentrates daily The animals were randomly allocated to three equally sized treatment groups, each containing 11 sheep. The sheep were diagnosed to have ORC based on clinical examination (Lacasta et al., 2019).

Briefly, the presence of cough, nasal discharge, and abnormal lung sound on auscultation are the major findings. In addition, evidence of systemic signs was confirmatory. Systemic signs were fever (≥ 40°C), anorexia, and depression. The present clinical trial was conducted according to the CONSORT statement guidelines (2010).

Table 1. Description and scores of clinical signs in sheep with acute respiratory disease

	Clinical variable	Level and description
1	Cough	Absent: 0 Dry cough: 1 Moist cough: 2
2	Nasal discharge	Absent: 0 Serous discharge: 1 Mucoid discharge: 2 Mucopurulent: 3 Purulent: 4
3	Ocular discharge	Absent: 0 Serous discharge: 1 Mucoid discharge: 2 Purulent: 3
4	Heart rate (beat/min)	70-90: 0 90-100: 1 100-120: 2 >120: 3
5	Respiratory rate (cycle/min)	20-40: 0 40-50: 1 50-60: 2 >60 : 3
6	Temperature	39-40^{0}C: 0 >40-41^{0}C: 1 >41-42^{0}C : 2 >42^{0}C : 3
7	Appetite	Inappetance: 1 Anorexia:2
8	Alertness	Alert: 0 Mild depression: 1 Severe depression: 2
9	Dyspnea	Absent: 0 Mild dyspnea: 1 Severe dyspnea: 2
10	Lung sound	Normal sound: 0 exaggerated vesicular sound: 1 wheezes: 2 crackles: 3
11	Conjunctivitis	Absent: 0 Mild conjunctivitis: 1 Severe conjunctivitis: 2

Treatment protocol

Group 1 received subcutaneous injections of Amoxicillin LA at a dosage of 15 mg/kg body weight, administered three times successively with a 48-hour interval between each injection (El-Deeb et al., 2021), and intramuscular administration of meloxicam **(**METACAM, Boehringer Ingelheim Animal Health, USA Inc.) at a dosage of 1 mg/kg body weight for five consecutive days (Metacam, 2016). Group 2 received treatment that involved subcutaneous administration of Amoxicillin LA (Amoxypen LA, MSD Animal Health) at a dosage of 15 mg/kg body weight, for three successive times 48 hours apart, and intravenous administration of phenylbutazone (Buta-Fenil, AM Trading, Lab. Tornel, Mexico) at a dose of 4 mg/kg body weight for five consecutive days (El-Deeb et al., 2021). Group 3 was treated only with Amoxicillin LA, at the same dose and protocol as group 1 and group 2.

Clinical follow-up

To assess the health of the sheep, clinical examination and clinical index scores were recorded for each animal on the first day of the visit (T0), day 7 (T1), and day 14 (T2) post-treatment.

Blood samples

Two blood samples were collected from each sheep under investigation through jugular vein puncture. While sampling, no sedative drugs have been used. Sampling was performed at the time of the first visit and on days 7 and 14 post-treatment. One of the blood samples (5 ml) was collected on anticoagulant (5 mg sodium ethylene diamine tetra acetic acid) for the evaluation of total and differential leukocytic counts. The second five mL of blood sample was collected without anti-coagulant for analysis of biochemical parameters including iron, zinc, copper, haptoglobin, albumin, total protein, and globulin concentrations.

Hematological analysis

The red blood cell (RBCs, 10^6/µl), hemoglobin (Hb, gm/dl), PCV%, total leukocytic, and differential leukocyte (WBCs10^3/µl) counts were determined using a hematology analyzer (MS9-5, Melet Schloesing Laboratories, France) according to (Feldman et al., 2000).

Biochemical examination

Iron was measured colorimetrically using commercial test kits (Fortess Diagnostics Limited Co., United Kingdom). Zinc and copper levels were estimated colorimetrically using commercial test kits (Biodiagnostic Co., Egypt). Albumin and total protein levels were measured colorimetrically using commercial test kits (Stanbio, Boerne). Finally, haptoglobin was measured by the nephelometric method using commercial test kits (Turbox, Orion diagnostica Oy, Finland). Nephelometry was applied as a simple, accurate, and reliable technique for the determination of haptoglobin (Shih et al., 2014). The haptoglobin was measured at a wavelength of 600 nm following the instruction of the manufacturer of the used test kits.

Statistical analysis

A commercial software program (GraphPad version 5.0, USA) was used for statistical analyses. First, the groups were assessed for homogeneity using the Kruskal–Walli's test. As the data were found to be homogenous, the mean and standard deviation for variables were presented. For the clinical index score, analysis of variance test (ANOVA) and Bonferroni multiple comparison tests as post hoc was performed to find the significant changes. A general linear model with repeated measures ANOVA was used to evaluate the effect of anti-inflammatory drugs on biochemical variables. Wilks' lambda test was used as an indicator of significant changes. Where such a test was found to be significant, analysis of variance test (ANOVA) and Tukey's comparison test as post hoc was performed. For all data, the outcomes were considered significant when $p < 0.05$.

RESULTS

The clinical disease index score indicated that significant improvement in sheep treated with a combination of meloxicam and amoxicillin LA in group 1, compared to those treated with a combination of amoxicillin LA and phenylbutazone in group 2 and those treated with amoxicillin LA alone in group 3. This improvement was significant on 7 ($p < 0.01$) and 14 ($p < 0.01$) days post-treatment. Furthermore, complete recovery was achieved in the sheep of group 1 with a clinical index score of 1, whereas the sheep of groups 2 and 3 had clinical index scores of six and seven, respectively, 14 days post-treatment. The respiratory rate and heart rate returned to normal levels in sheep of group 1 and group 2 more rapidly than those of group 3.

The red blood cell indicated Hb concentration, RBC count, and MCHC% significantly increased in sheep of group 1, compared to those of groups 2 and 3 at 14 days post-treatment ($p < 0.01$; Figure 1). However, the total leukocyte count significantly decreased in the sheep of group 1, compared to those of group 3 on 14 days post-treatment ($p < 0.01$). The neutrophil percentage significantly decreased in sheep of group 1, compared to those of group 2 and group 3 on 7 days and 14 days post-treatment ($p < 0.05$). In contrast, lymphocyte percentage was significantly higher in sheep of group 1 compared to those of group 2 and group 3 on 7 days and 14 days post-treatment ($p < 0.05$; Figure 2). Serum haptoglobin showed a significant decrease in sheep in group 1, compared to those of group 2 and group 3 on 7 days and 14 days post-treatment ($p < 0.01$; Figure 3). Similarly, serum globulin revealed a significant decrease in sheep of group 1, compared to those of group 3 on 14 days post-treatment ($p < 0.05$). Both serum albumin and albumin/globulin (A/G) ratio indicated a significant increase in sheep of group 1 compared with those of group 3 on 14 days post-treatment ($p < 0.05$; Figure 4). Serum iron levels rose significantly in sheep of group 1 compared with those of group 3 on 14 days post-treatment ($p < 0.05$; Figure 5). However, the serum copper levels in sheep of group 1 demonstrated a significant decrease, compared to those of group 3 on 7 and 14 days post-treatment ($p < 0.05$; Figure 6). Serum zinc levels significantly increased in sheep of group 1, compared to those of group 3 on 14 days post-treatment ($p < 0.05$), and significantlyincreased compared to those of groups 2 and 3 on 14 days post-treatment ($p < 0.05$; Figure 7).

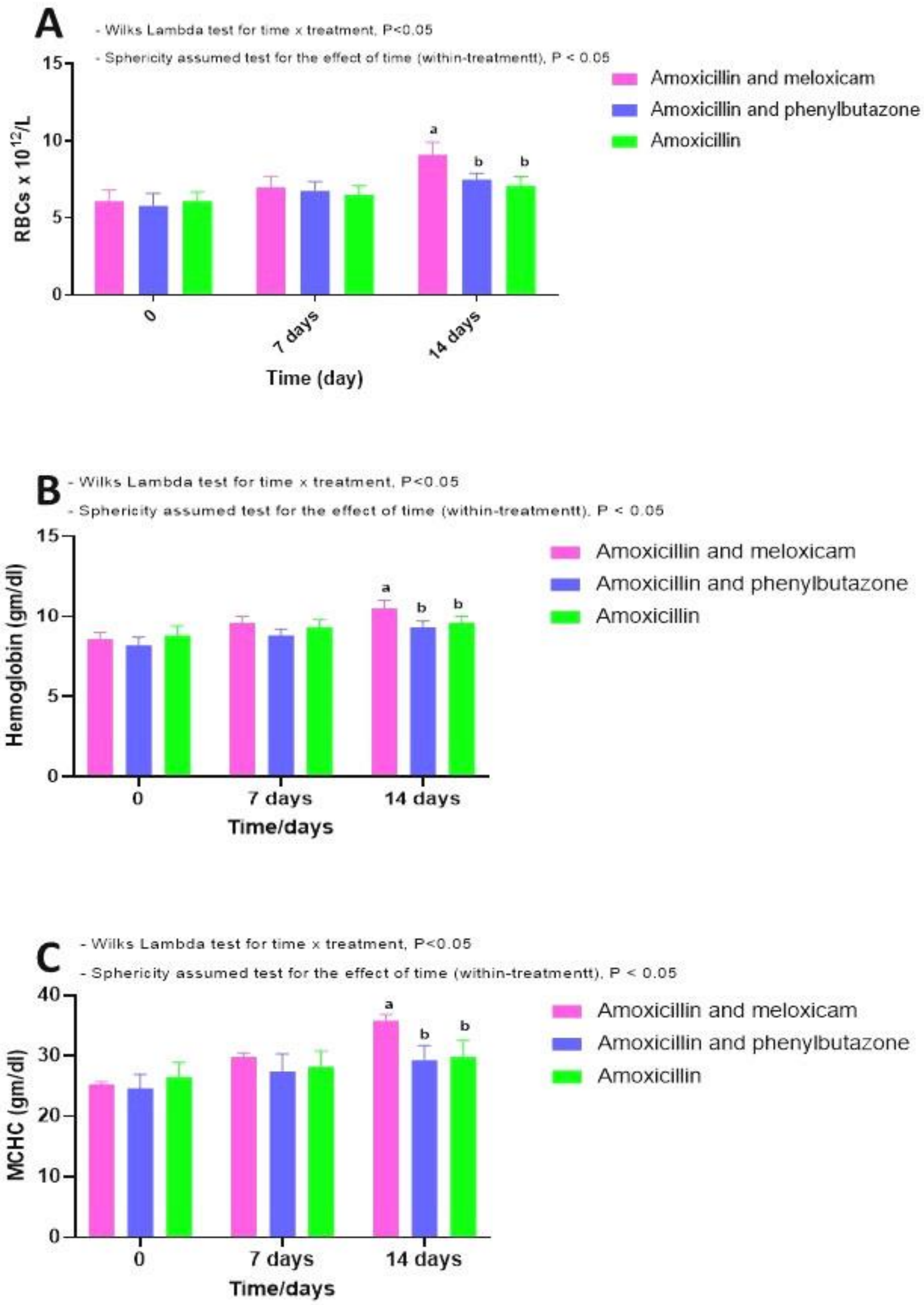

Figure 1. Mean values of hematological indices in sheep with ovine respiratory disease before and after treatment with amoxicillin LA and meloxicam, amoxicillin LA and phenylbutazone and with amoxicillin LA alone. [a,b:] Means with different superscript letters are significantly different at $p < 0.05$.

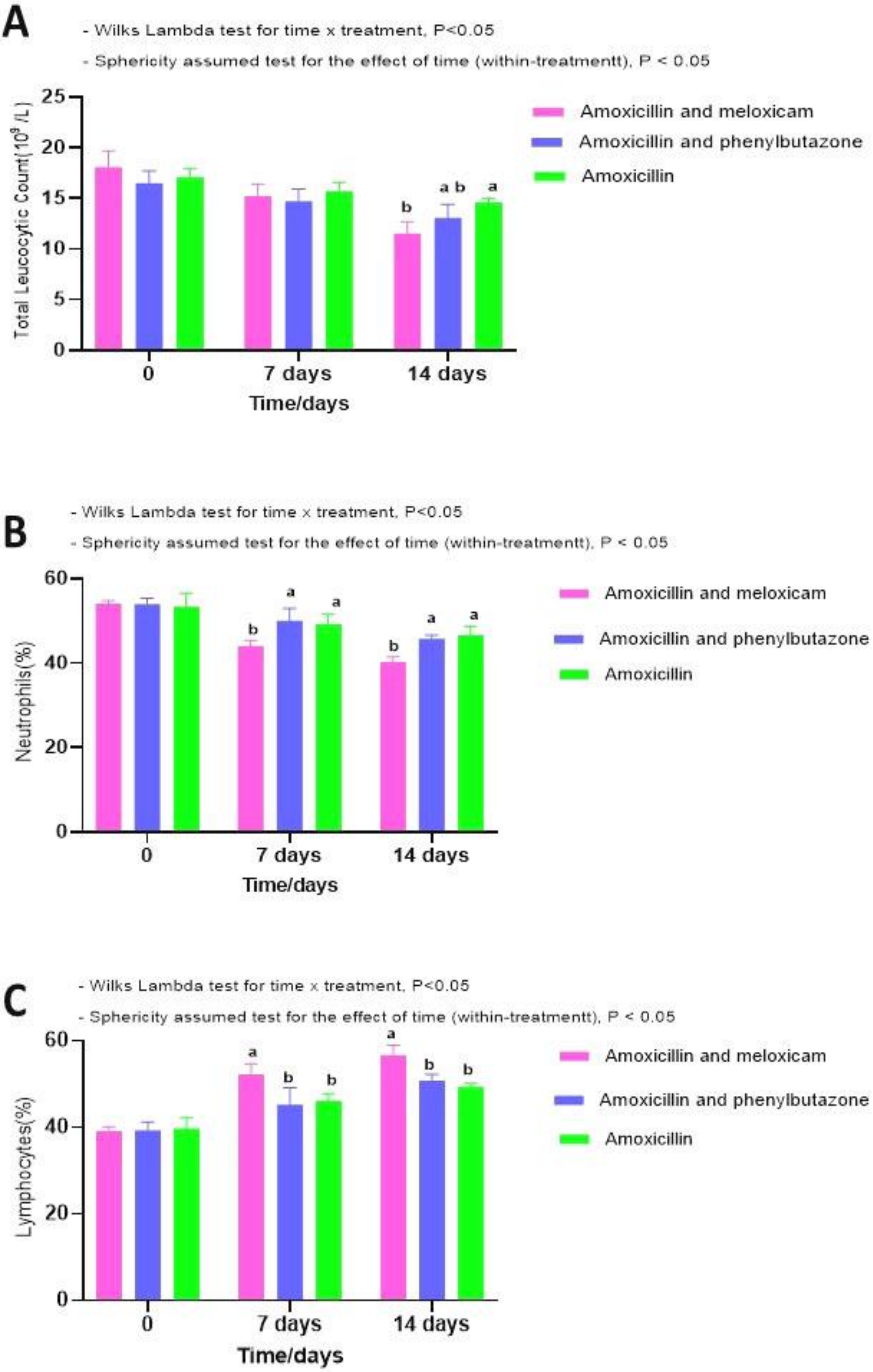

Figure 2. Mean values of total and differential leukocytic count in sheep with ovine respiratory disease before and after treatment with amoxicillin LA and meloxicam, amoxicillin LA and phenylbutazone and with amoxicillin LA alone. [a,b:] Means with different superscript letters are significantly different at $p < 0.05$.

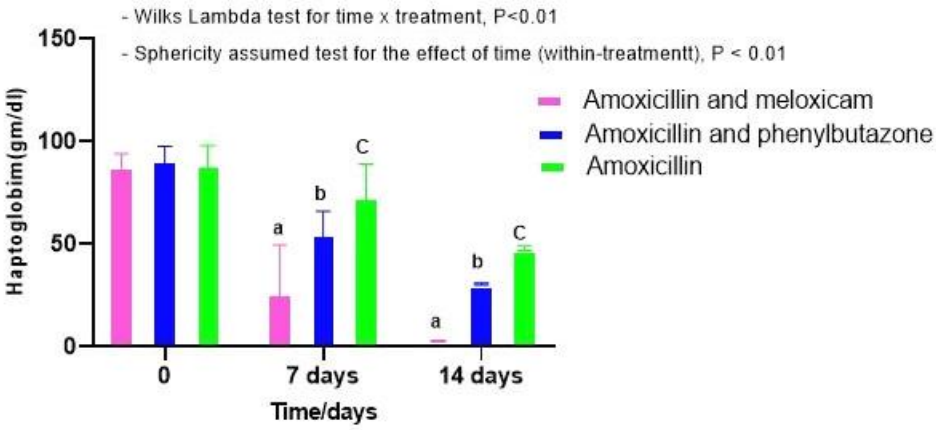

Figure 3. Mean values of haptoglobin in sheep with ovine respiratory disease before and after treatment with amoxicillin LA and meloxicam, amoxicillin LA and phenylbutazone and with amoxicillin LA alone. [a,b,c:] Means with different superscript letters are significantly different at $p < 0.05$.

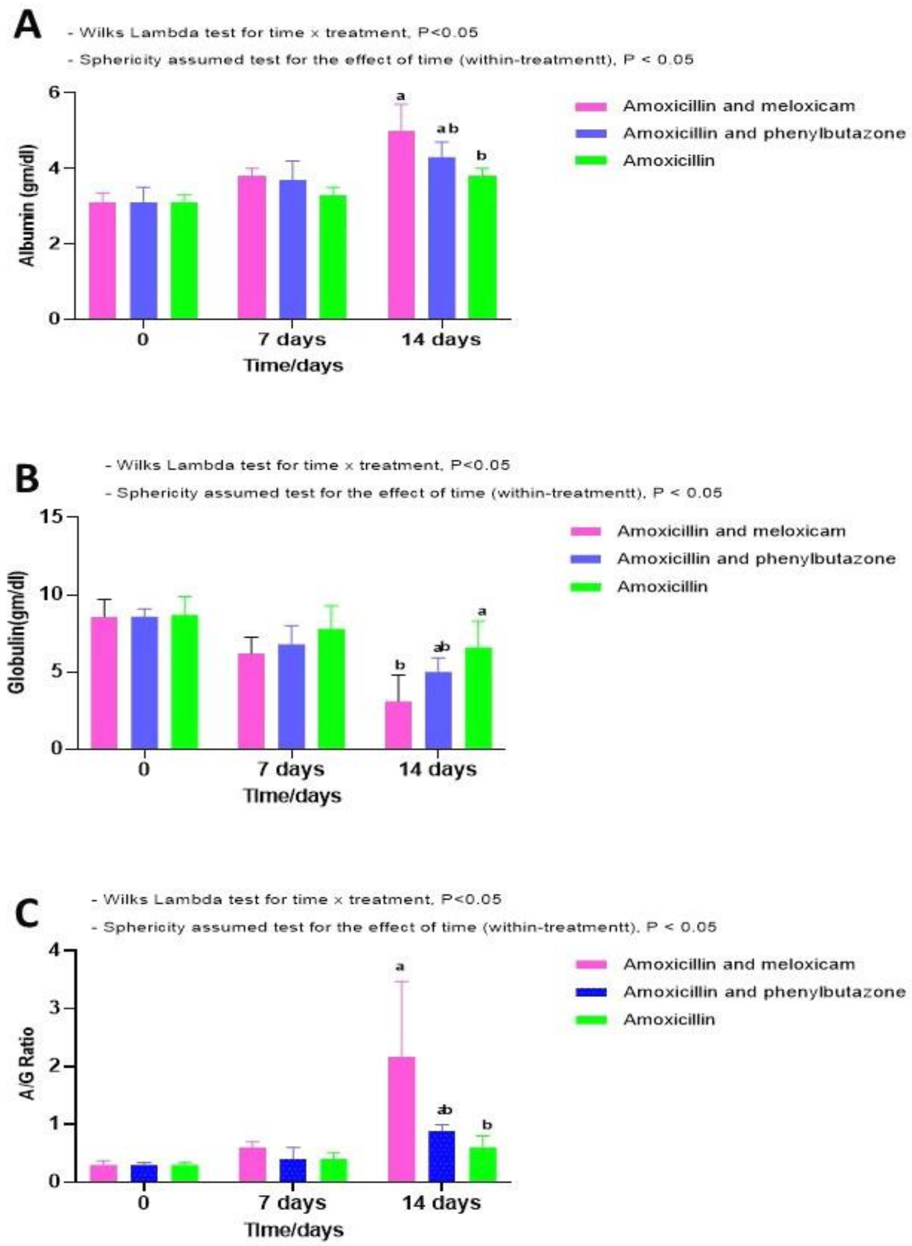

Figure 4. Mean values of serum protein in sheep with ovine respiratory disease before and after treatment with amoxicillin LA and meloxicam, amoxicillin LA and phenylbutazone and with amoxicillin LA alone. [a,b:] Means with different superscript letters are significantly different at $p < 0.05$.

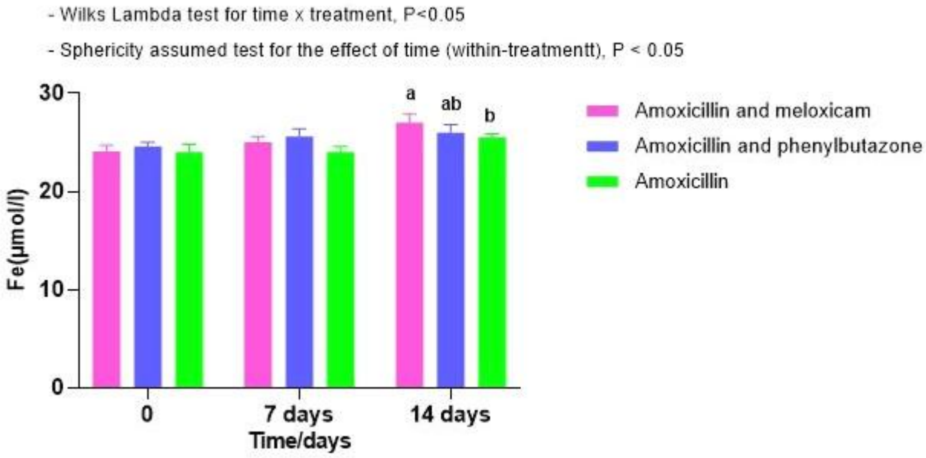

Figure 5. Mean values of serum iron in sheep with ovine respiratory disease before and after treatment with amoxicillin LA and meloxicam, amoxicillin LA and phenylbutazone and with amoxicillin LA alone. [a,b:] Means with different superscript letters are significantly different at $p < 0.05$.

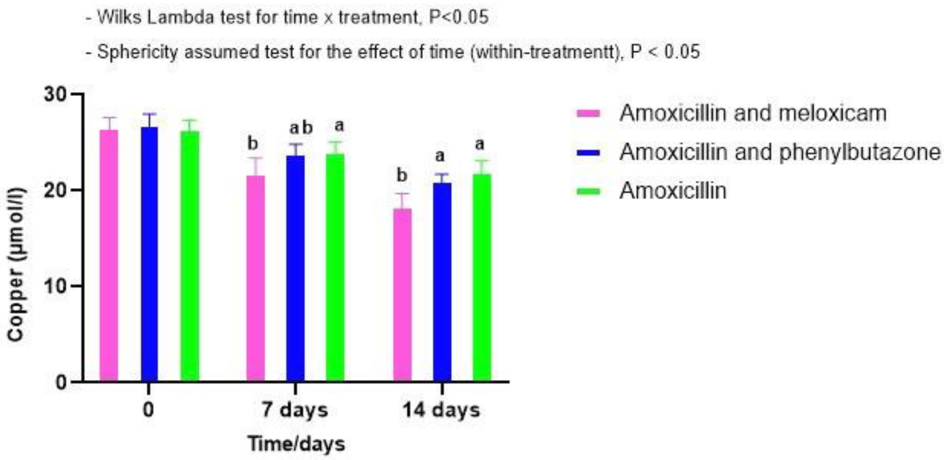

Figure 6. Mean values serum copper in sheep with ovine respiratory disease before and after treatment with amoxicillin LA and meloxicam, amoxicillin LA and phenylbutazone and with amoxicillin LA alone. [a,b,:] Means with different superscript letters are significantly different at $p < 0.05$.

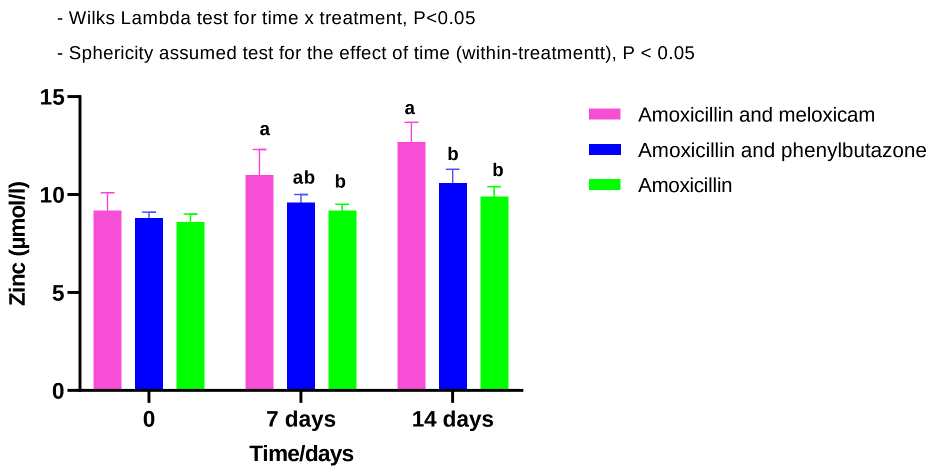

Figure 7. Mean values serum zinc in sheep with ovine respiratory disease before and after treatment with amoxicillin LA and meloxicam, amoxicillin LA and phenylbutazone and with amoxicillin LA alone. [a,b:] Means with different superscript letters are significantly different at $p < 0.05$.

DISCUSSION

In the present study, significant improvement in the clinical index score was recorded in sheep treated with meloxicam compared to those treated with phenylbutazone and those treated with Amoxicillin LA alone. This finding is consistent with that of Bednarek et al. (2003) who stated that administering a combination of oxytetracycline and meloxicam to calves with enzootic bronchopneumonia led to a significantly faster improvement in the clinical illness index score than treatment with a combination of oxytetracycline and flumethasone, or oxytetracycline alone. Additionally, Friton et al. (2005) found that administering a combination of meloxicam and antibiotics to feedlot cattle with bovine respiratory disease resulted in an improvement of clinical signs and a reduction of lung lesions compared to those treated with antibiotics alone. Similarly, Georgoulakis et al. (2006) observed that combining meloxicam with chlortetracycline in the treatment of growing pigs with porcine respiratory disease complex infection resulted in quicker recovery from respiratory inflammation caused by viruses and bacteria compared to pigs treated with chlortetracycline alone.

According to Dudek et al. (2020), an increase in neutrophil levels is typically observed during the onset of pneumonia in calves. Neutrophils play a crucial role in defense mechanisms through phagocytosis and oxidative burst (Jimbo et al., 2017). Therefore, the significant decrease in neutrophils and increase in lymphocyte percentage observed in the group of sheep treated with meloxicam compared to the other treatment groups may be due to the anti-inflammatory effect of meloxicam.

Concerning APPs, meloxicam could significantly decrease serum haptoglobin and globulin but increase serum albumin and albumin/globulin (A/G) ratio compared to phenylbutazone and Amoxicillin LA alone. This finding suggests rapid recovery and improvement in meloxicam treated group than others. Haptoglobin is an acute-positive protein that is a clinically relevant criterion for evaluating the occurrence and severity of inflammatory reactions in cattle, such as pneumonia (Eckersall and Bell, 2010). It is a scavenger protein with antioxidant, antimicrobial, and anti-inflammatory (Gulhar et al., 2018). The anti-inflammatory effect of haptoglobin is due to its ability to bind with CD11b/CD18 proteins which are found on neutrophils (El Ghmati et al., 1996). Additionally, other plasma proteins (albumin and globulin) play an essential role in the inflammation process and are usually used to evaluate the level of malnutrition and the seriousness of an illness (Laky et al., 2007). Albumin is considered the primary negative APP found in all animal species (Cray et al., 2009). According to Aldred and Schreiber (2020) during inflammation, albumin synthesis decreases, and amino acids are utilized for the creation of positive APPs. In addition, Otal et al. (2022) attributed the decreased serum albumin levels during inflammation to an increase in the volume of distributed albumin due to increased capillary permeability, leading to the escape of serum albumin. In contrast, elevated levels of globulin are associated with chronic inflammation and indicate prolonged exposure to various proinflammatory cytokines (Gopal et al., 2010). Furthermore, the significant increase in globulin in bovine respiratory disease-affected calves may be due to immune system activation caused by pathogens (Abd El-Raof and Hassan, 1999). The A/G ratio, a biomarker that combines albumin and globulin, indicates the status of inflammation and nutrition (Yang et al., 2022). Various respiratory disorders have also been associated with A/G abnormalities in patients with respiratory diseases (Qin et al., 2018; Chen et al., 2022).

Regarding copper, zinc, and iron meloxicam-treated sheep recovered their normal level of copper, zinc, and iron earlier than those of phenylbutazone and Amoxicillin LA groups. This finding may be attributed to the potent anti-inflammatory effect of meloxicam. Generally, in farm animals, as a result of infection and toxemia, there is hypozincemia, hypoferremia, and hypercupremia (Constable et al., 2016). Moreover, infection in farm animals is found to be associated with oxidative stress (Lykkesfeldt and Svendsen, 2007). The increased serum level of copper before treatment may be due to an increase in the production of the copper-binding protein, ceruloplasmin. This protein scavenges free radicals and acts as an antioxidant during infection and inflammation (Fox et al., 1995). In calves, Galarza et al. (2021) attributed the decrease in serum zinc levels during infection to the release of interleukin 1β and interleukin 6. In mice, the release of cytokines during infection has been found to facilitate Zinc uptake from the bloodstream (Aydemir et al., 2012). Additionally, decreased hepatic production of albumin (transporting zinc), transferrin, and lactoferrin leads to lower levels of zinc and iron in the blood (Gruys et al., 2005). In a study, it has been demonstrated that meloxicam could ameliorate the oxidative stress caused by extraneous exercise by strengthening the superoxide dismutase activity (Gunes et al., 2011). However, the combination of meloxicam and injectable trace elements did not affect the morbidity and serum levels of trace element on 45 days post-treatment in fattening calves (Hartschuh, 2015).

CONCLUSION

In conclusion, meloxicam-treated sheep had earlier clinical recovery and early normalization of blood parameters than those treated with phenylbutazone or amoxicillin LA alone. Meloxicam is an alternative effective anti-inflammatory drug for sheep in clinical practice. Further studies are needed to investigate the effect of meloxicam on specific infections in sheep with respiratory signs and to evaluate the cytokine response to treatment with meloxicam.

DECLARATIONS

Acknowledgments

The authors would like to thank the dean of Scientific Research, Vice Presidency for Graduate Studies and Scientific Research, King Faisal University for supporting this study.

Authors' contributions

Abdullah Khalid Alwayel did the conceptualization and drafting of the manuscript, Mohamed Marzok supervised the project and manuscript submission, Magdy Gioushy conducted the investigation and drafting of the manuscript; Mahmoud Kandeel and Adel Almubarak did project administration and resources; Yaser Hamad did data analysis; Saad Shousha did interpretation and writing, Sabry El-khodery did editing and reviewing of the manuscript. All authors have read and agreed to the published version of the manuscript.

Competing interests

There are no competing interests to disclose.

Ethical considerations

Ethical issues (including plagiarism, consent to publish, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancy) have been checked by all the authors.

Funding

This study was funded by Deanship of Scientific Research, Vice Presidency for Graduate Studies and Scientific Research, King Faisal University [Fund number: KSA 5337].

Availability of data and materials

All data of this study are available by reasonable requests from authors.

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