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Effect of Oxytetracycline and Vitamins on the Restoration of Altered Hematological Profile of Cattles Clinically Infected with Lumpy Skin Disease (LSD) Virus

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ABSTRACT

Lumpy skin disease (LSD) is a serious disease of cattle. The study was conducted to explore the potential protective effect of Oxytetracycline and Vitamins A, D and E on hematological alterations induced by lumpy skin virus in clinically infected animals. Significant changes were observed in the percentages of white blood cells (WBC), granulocytes (GRAN), lymphocytes (LYMP), Hematocrit (HCT), mean corpuscular hemoglobin concentration (MCHC) and mean platelets volume (MPV) in some infected animals. Lumpy skin disease caused a significant reduction in WBC count (4.44 ± 0.45), as compared to healthy non-infected animals (6.90 ± 0.54). Treatment with Oxytetracycline alone increased the number of WBC, indicating its antiviral properties. However, adjunct treatment with vitamin A, D, and E did not impact WBC restoration. Lymphocyte count spiked (from 0.70 ± 0.12 to 1.8583 ± 0.18) in response to lumpy skin infection, reflecting the disease's inflammatory and viremic nature. Granulocytopenia was observed in infected animals, potentially due to the lack of innate immunity against the virus. Hematocrit percentage was significantly higher (30.13 ± 1.48) in infected animals indicating dehydration, but decreased in the Oxytetracycline treated group (26.68±1.84), suggesting restoration of appetite and hydration. Increased mean corpuscular volume (47.06 ±1.73) was observed in infected animals as compared to non-infected animals (42.49 ±1.38). Treatment with Oxytetracycline alone or in combination with vitamins showed potential in restoring red blood cell size. Decreased mean corpuscular hemoglobin concentration (MCHC) was observed in lumpy skin infected animals, and treatment effectively restored MCHC. In conclusion, lumpy skin disease caused significant hematological alterations, and treatment with Oxytetracycline alone or in combination with Vitamins A, D and E showed promising results in restoring the affected parameters.

INTRODUCTION

Lumpy skin disease (LSD, Pseudo-urticaria, Neethling virus disease, exanthema nodularis bovis, and knopvelsiekte) is an infectious disease (Al-Salihi, 2014). The virus causing lumpy skin disease belongs to the family Poxviridae. The disease caused a major economic loss to livestock industry including to skin damage, infertility, mastitis, reduced milk and meat production and mortality (Imran *et al*., 2022). Moreover, the pathological aspects of this disease have also been reported in the immunological, biochemical and hematological parameters of the affected animals (Neamat-Allah, 2015).

Antibiotics are linchpin in livestock husbandry for prophylactic, metapylactic and therapeutic purpose (Bousquet-Mélou *et al*., 2010). The important antibiotics used for treatment and prevention of livestock diseases are penicillin, streptomycin, amoxicillin, enrofloxacin, spiramycin, gentamycin, lincomycin, trimethoprim, sulphadiazine, colistin, tylosin, lincomycin, ceftiofur sodium and Oxytetracycline. Of these being a broad spectrum antibiotic, Oxytetracycline have many other properties of physiological and therapeutic importance in inflammation, tissue remodeling, metastatic action of

tumors, embryogenesis, anti-proteolysis, oxidative stress and leukocytic migration (Rohde *et al*., 1999; Nagase and Woessner, 1999; Mosquera-Sulbaran and Hernández-Fonseca, 2021; Esterly *et al*., 1984). The evidence of tetracycline to be antiviral dates to 1960 and 1970 (Mosquera-Sulbaran and Hernández-Fonseca, 2021). Moreover, many of the results of experimental and clinical trials have demonstrated that tetracycline compounds could be used as drug of choice in the therapeutics of viral infections such as Venezuelan equine encephalitis (Negrette and Mosquera, 1995). Flavivirus infection, vesicular stomatitis virus (Takaoka *et al*., 2003). Japanese encephalitis virus (Fujioka *et al*., 2004).Virus induced apoptosis (Michaelis *et al*., 2007). Crimean Congo hemorrhagic fever (Sharifi et al., 2017). Dengue virus (Lai et al., 2018) and respiratory syncytial virus (Bawage *et al*., 2019).

Vitamins and minerals are vital for robust and well-built immune system and supplementation of vitamins and minerals has enhancing effects on innate, cell mediated and antibody-mediated immunity against viral infections (Samad *et al*., 2021). Vitamin A supplementation diet can boost up serum levels of IgG, IgM, and IgA antibodies. Moreover, vitamin A is therapeutically effective in the treatment of various infectious diseases (Huang *et al*., 2018). The important antiviral aspect of vitamin D is the induction of antimicrobial peptides. These antimicrobial peptides eliminate viruses in addition to bacteria (Wang *et al*., 2004). The length and severity of dengue can be reduced by oral administration of vitamin D (Sánchez-Valdéz *et al*., 2009). Lower levels of vitamin D in blood may be associated with an increased risk of respiratory tract infections (Ginde *et al*., 2009). Vitamin E is another important fat soluble vitamin playing an utmost important role in regulation and modulation of immune system (Jayawardena *et al*., 2020). Vitamin E supplementation can modulate immune function and hence affects host susceptibility to infectious diseases (Lewis *et al*., 2019).

In this study we investigate the effect Oxytetracycline alone or in combination with fat soluble vitamins on the hematological profile of lumpy skin disease (LSD) cattle.

MATERIALS AND METHODS

Animal Welfare

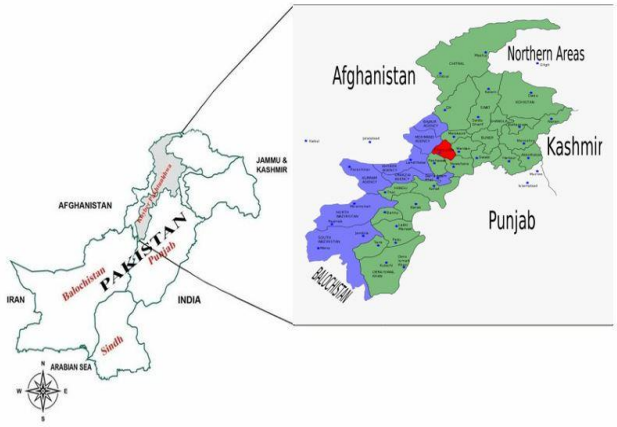
All sampling procedures related to this study were in accordance with all applicable institutional, local, and national guidelines and laws. Owners of the cows included in the study were provided with information about the study. They willingly allowed the use of their samples for future research.

Study Area

This research study was carried out in district Charsadda, Khyber Pakhtunkhwa, Pakistan between December 2022 and January 2023 (Figure 1).

Figure 1

Map of Study Area District Charsadda, Khyber Pakhtunkhwa, Pakistan.



Experimental Design

A total of sixty (60) cows were investigated in this study, including 20 healthy cows and 40 naturally infected cows with lumpy skin disease in the field condition. All the cows were divided into three groups (Group A, Group B, and Group C) with each group consisting of 20 cows. The healthy cows in Group A were given no treatment, while the infected cows in Group B were treated with Oxytetracycline-200 (OX LA-20%) as per the manufacturer's recommendation (1ml/10kg body weight on alternate days for 5 days). The infected cows in Group C were treated with Oxytetracycline-200 (OX LA-20%) in adjunction with Vitamins A, D, E (VAD3) as per the manufacturer's recommendation (1ml/10kg body weight on alternate days for 5 days).

Sampling

Blood samples were collected from healthy cows once and from LSD infected cows twice (before and after treatment). The blood samples were collected by jugular venipuncture using a 16G veterinary needle. Before collection, the animals were properly restrained, and the collection site was disinfected with absolute alcohol. The jugular vein was occluded by applying pressure in the jugular groove located in the lower neck, and the needle attached to a 5ml syringe was inserted into the distended jugular vein at a 45° angle cranial to the jugular groove. Blood (3ml) was collected and dispensed into anticoagulant-coated tubes (Sharma and Singh, 2008). The tubes were labeled for identification of animals, and duplicate samples from each animal were collected. The collected blood samples were kept in an ice box and shifted to Veterinary Research Institute (VRI) Peshawar for laboratory analysis.

Laboratory Analysis

The blood samples were analyzed for hematological parameters such as Hb, MCH, PCV, WBC, and RBC using a Hematology analyzer (URIT-2900 plus) at Veterinary Research Institute (VRI), Peshawar, Khyber Pakhtunkhwa Pakistan.

Statistical Analysis

Different hematological parameters from laboratory results were analyzed computing descriptive statistics such as graphical analysis and descriptive measures were analyzed by using the Statistical Package for the Social Sciences (SPSS, version 22.0), and *P* value less than 0.05 was considered significant.

RESULTS

Effect of Oxytetracycline on the Erythrogram of Lumpy Skin Disease Affected Cattle

Our result showed that The HCT levels was higher ($P \leq 0.05$) in BT_OXY (PC) group (infected animal without treatment) than the healthy/control (NC) and AT_OXY_ Rx (after treatment of Oxytetracycline) groups. The MCHC level was higher ($P \leq 0.05$) in healthy/control (NC) and AT_OXY_ Rx (after treatment of Oxytetracycline) groups in comparison to the BT_ OXY (PC) group (infected animal without treatment).

The MPV level was higher ($P \leq 0.05$) in the BT_ OXY (PC) group (infected animal without treatment) and AT_OXY_ Rx (after treatment of Oxytetracycline) than the healthy/control (NC) group. The RBC, HGB, MCV and MCH, did not vary among the treated and control (NC and PC) groups as shown in Table 1.

Table 1

Effect of Oxytetracycline on Erythrogram of Lumpy Skin Disease (LSD) Affected Cattle.

Parameters	Healthy Control (NC)	BT (PC)	AT.OXY	*P*-Value
RBC	5.39 ± 0.40	6.42 ± 0.23	6.12±0.49	0.122
HGB	8.44 ± 0.50	9.35 ± 0.30	9.19± 0.52	0.310
HCT	22.36 ± 0.98^{b}	30.13 ± 1.48^{a}	26.68±1.84^{ab}	0.001
MCV	42.49 ±1.38	47.06 ±1.73	44.11 ±1.07	0.088
MCH	15.77 ± 0.34	14.58 ± 0.25	15.35±0.95	0.228
MCHC	37.49 ± 0.63^{a}	31.33 ± 0.89^{b}	35.05±2.26^{ab}	0.003

Effect of Oxytetracycline on the Leukogram of lumpy skin disease affected Cattle

The current finding showed that WBC concentration was higher ($P \leq 0.05$) in healthy/control (NC) group than the BT_ OXY (PC) group (infected animal without treatment) and AT_OXY_ Rx (after treatment of Oxytetracycline). The LYM concentration was higher ($P \leq 0.05$) in the BT_ OXY (PC) group (infected animal without treatment) and AT_OXY_ Rx (after treatment of Oxytetracycline) than the healthy/control (NC) group. The granulocytes concentration was higher ($P \leq 0.05$) in healthy/control (NC) group than the BT_ OXY (PC) group (infected animal without treatment) and AT_OXY_ Rx (after treatment of Oxytetracycline). The mid-range absolute counts (MID) of WBC's other than lymphocytes and granulocytes, red cells distribution width (RDW_CV) and platelets (PLT) did not vary among the treated and control (NC and PC) groups as shown in Table 2.

Table 2

Effect of Oxytetracycline on Leukogram of Lumpy Skin Disease (LSD) Affected Cattle.

Parameters	Healthy Control (NC)	BT (PC)	AT.OXY	*P*-Value
WBC	6.90 ± 0.54^{a}	4.44 ± 0.45^{b}	4.87 ± 0.63^{b}	0.004
LYM	0.70 ± 0.12^{b}	1.8583 ± 0.18^{a}	2.27±0.31^{a}	0.001
MID	1.80 ±0.30	1.35 ± 0.17	1.38±0.16	0.376
GRAN	4.40 ±0.30^{a}	1.23 ± 0.22^{b}	1.22±0.25^{b}	0.001
RDW_CV	19.60 ± 0.34	19.20 ± 0.30	20.70±1.77	0.487
PLT	178.21±11.75	166.66±18.11	387.55±201.19	0.207
MPV	10.06 ± 0.32^{b}	11.65 ± 0.25^{a}	11.53 ± 0.96^{a}	0.007

Effect of Oxytetracycline and Vitamins on the Erythrogram of Lumpy Skin Disease Affected Cattle

The current results showed the MCV level was higher ($P \leq 0.05$) in BT_OXY+VIT (PC) group (infected animal without treatment) than the healthy/control (NC) group and AT_OXY +VIT-Rx group (infected animal treatment with Oxytetracycline and vitamins). The MCHC level was increased higher ($P \leq 0.05$) in healthy/control (NC) and AT_OXY +VIT-Rx (after treatment of Oxytetracycline) groups than the BT_OXY+VIT (PC) group (infected animal without treatment).

The GRAN, RBC, HGB, MCH and HCT did not vary among the treated group and healthy/ control group as shown in Table 3.

Table 3

Effect of Oxytetracycline Plus Vitamin on Erythrogram of Lumpy Skin Disease (LSD) Affected Cattle.

Parameters	Healthy/Control (NC)	BT (PC)	AT OXY +VIT	*P*-Value
RBC	5.38±0.40	4.97 ± 0.15	5.14 ± 0.13	0.706
HGB	8.44± 0.51	8.49 ± 0.27	8.84 ± 0.45	0.848
HCT	22.36±0.98	25.36 ± 1.20	22.54 ± 2.82	0.383
MCV	42.49±1.38^{b}	51.34 ± 2.78^{a}	49.34 ±2.80^{b}	0.010
MCH	15.77±0.34	17.11 ± 0.71	17.17 ± 0.78	0.111
MCHC	37.49 ±0.63^{a}	33.63 ± 1.01^{b}	35.11 ± 1.17^{ab}	0.011

Effect of Oxytetracycline and Vitamins on the Leukogram of Lumpy Skin Disease Affected Cattle

The MPV level was increased ($P \leq 0.05$) in BT_OXY+VIT (PC) group (infected animal without treatment) than the healthy/control (NC) group and AT_OXY +VIT-Rx group (infected animal treatment with Oxytetracycline and vitamins). The WBC, LYM,

MID, RDW-CV, and PLT did not vary among the treated group and healthy/ control group as shown in Table 4.

Table 4
Effect of Oxytetracycline Plus Vitamins on Leukogram of Lumpy Skin Disease (LSD) Affected Cattle.

Parameters	Healthy/Control (NC)	BT (PC)	AT OXY +VIT	*P-Value*
WBC	6.90 ± 0.54	5.34 ± 0.88	5.589 ± 0.59	0.184
LYM	0.70 ± 0.12	0.99 ± 0.20	1.17 ± 0.24	0.175
MID	1.80 ± 0.32	1.54 ± 0.40	1.57 ± 0.45	0.867
GRAN	4.40 ± 0.33	3.1429 ± 0.94	2.84 ± 0.36	0.083
RDW_CV	19.60 ± 0.34	22.06 ± 2.40	19.12 ± 0.50	0.207
PLT	178.21 ± 11.75	141.88 ± 22.49	17.00 ±16.35	0.274
MPV	10.05 ± 1.22^{b}	12.30 ± 1.01^{a}	11.37 ± 1.80^{ab}	0.032

DISCUSSION

Lumpy skin disease is considered a transboundary animal disease due to its significant impacts on trade and food security as well as its capacity to spread to other countries (Rossiter and Al Hammadi, 2009). LSDV was treated with Oxytetracycline alone or with fat soluble vitamin.

Our results showed that lumpy skin disease caused a significant reduction in the number of WBC from 6.90 ± 0.54 to 4.44 ± 0.45. It has been reported by many researchers that the number of WBC usually decreased in response to viral infections (Korppi *et al*., 1993). The reason for low granulocytes in infected and treated group is also a viral infection. The count of WBC rebounded when body recovers from viral infections. Treatment of infected animals with Oxytetracycline significantly ($P \leq 0.05$) increased the number of WBC from 4.44 ± 0.45 to 4.87 ± 0.63. Hence it can be concluded that Oxytetracycline had antiviral properties eliminating enveloped viruses by production of anti-microbial peptides and prevention of viron formation as reported by (Mosquera-Sulbaran and Hernández-Fonseca, 2021). In other words, the depressing effect of lumpy skin disease virus was counteracted by antiviral action of Oxytetracycline. However, adjunct treatment of vitamin A, D and E with Oxytetracycline had no positive impact on restoration of WBC. The number of lymphocytes spikes in response to lumpy skin infection and a further increase in response to treatment of infected animals with Oxytetracycline. The number of lymphocytes usually increased in blood in response to a medical or pathological condition which caused inflammation, infection or a reaction to new medication (Cleveland Clinic- Health Essential News). It was reported that inflammatory levels in the environment greatly influenced the differentiation and activity of T-lymphocyte population (Moro-García *et al*., 2018). Lumpy skin disease is viral disease inducing inflammatory response in infected animals. Therefore, the viremia and inflammatory nature of the disease induced a spike in lymphocyte population. Moreover, the swelling and inflammation of lymph nodes in the disease was also a predisposing cause of lymphocytosis. The overall springing out of lymphocytes into action was aimed to neutralize the infection and inflammation. Although statistically non- significant but adjunct treatment of vitamins with Oxytetracycline numerically improved the number of lymphocytes. The mid-range absolute counts (MID) were rare types of WBC which was not classified as lymphocytes or granulocytes. Non-significant changes in the values of MID were observed between healthy, infected and treated group (OXY group and OXY+ VIT group). Significant changes in the level of granulocytes were observed between healthy and infected animal groups. Lumpy skin infection induces granulocytopenia in infected animals as compared to healthy animals. However, no difference was noted between infected and treated animal group. The possible reason for granulocytopenia may be that granulocytes were involved in innate immunity providing protection against non-specific pathogens (Keerthivasan *et al*., 2014). The infected animals had no innate immunity against lumpy skin virus. Therefore, there was no spike of granulocytes in response to infection. Hematocrit (HCT) percentage was significantly higher in infected animals as compared to healthy animals. Increased percentage of hematocrit may be due to dehydration of infected animals. There was also a significant difference in the percentage of hematocrit between infected and Oxytetracycline treated group. It indicated that restoration of animal appetite and hydration status. The increase in MCV (mean corpuscular volume) in infected animals was indication of liver damages and macrocytic anemia. The lumpy skin disease has been reported to cause damage to liver parenchyma (Shoulah *et al*., 2022). Oxytetracycline alone or in adjunction with vitamin A, D and E may have some role in restoring the normalcy of red blood cells size. A significant decrease in MCHC (mean corpuscular hemoglobin concentration) in infected animals was observed. Our findings of decreased MCHC in lumpy skin impacted animals were in line with that reported by (Abutarbush *et al*., 2015). Treatment with Oxytetracycline alone or in adjunction with vitamin A, D and E were equally effective in restoring MCHC Non -significant variations in red cells distribution width (RDW), platelets (PLT), and mean platelets volume (MPV) were observed.

CONCLUSION

The present study indicated that treatment with Oxytetracycline alone or in combination with fat soluble vitamins showed useful effects to restore the altered

hematological parameters of lumpy skin disease infected animals.

Novelty Statement

Lumpy skin disease is a viral infection of cattle. In this study, the potential protective effect of Oxytetracycline and Vitamins A, D and E has been evaluated with reference to hematological alterations induced by lumpy skin virus in clinically infected animals. We have found that lumpy skin disease results in significant hematological alterations, and treatment with Oxytetracycline alone or in combination with Vitamins A, D and E showed promising results in restoring the affected parameters in the field of veterinary in Khyber Pakhtunkhwa, Pakistan.

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***Authors' Contribution**

Jawad Ahmad: Investigation, Writing-original draft preparation.
Muhammad Aslam: Supervision.
Ali Gohar: Conceptualization.
Sulha Syed: Validation.
Shakirullah Khan: Software.
Huma Bahri & Muhammad Owais Khan: Data Curation.
Rafiq Ullah & Umar Hayat: Resources.
Mohsin Khan: Visualization.
Tahira Tayyeb & Zulfiqar Ali: Methodology.
Raheela Taj: Project administration.
Laraib Naseeb Khan: Formal analysis**.**
Asad Ullah: Writing-review and editing.

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