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Comparative Evaluation of Vincristine Sulfate and Vinblastine Sulfate for the Treatment of Transmissible Venereal Tumor in Dogs: A Pre-clinical and Pathological Study

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I and HJ designed the study. I and QU wrote the manuscript. MZK, FLL and MF supervised the manuscript. I, BM, SH and QU collected the sample. RM, RDM, Z and LAL edited and reviewed the final version of manuscript.

Key words
Canine transmissible venereal tumor (TVT), Vincristine sulfate, Vinblastine sulfate, chemotherapy, Clinical and pathological evaluation

ABSTRACT

Canine Transmissible Venereal Tumor (TVT) is a sexually transmitted, contagious neoplasia in dogs. This study aimed to investigate the clinical and pathological characteristics of the TVT and assess the efficacy of two chemotherapeutic treatments, vincristine sulfate and vinblastine sulfate, in treating TVT. A total of 20 dogs with TVTs randomly divided into two groups, A and B, each consisting of 10 dogs were included in this study. Group A received intravenous vincristine sulfate at a dose of 0.025 mg/kg for 2-5 weeks, while group B was treated with vinblastine sulfate at a dose of 0.1 mg/kg for 3-5 weeks. Blood samples were collected at the start of treatment and at various intervals thereafter for complete blood count analysis. The results showed a significant association between lymphocyte count and treatment duration for both vincristine sulfate and vinblastine sulfate. Similarly, the treatment duration had a significant effect on platelet and white blood cell concentrations ($P<0.05$) for both chemotherapeutic agents. Cytological examination revealed round to slightly polyhedral cells with grayish cytoplasmic appearance upon staining. Histopathological examination confirmed the presence of individual round cells with vesicular nuclei in TVTs. The study found that TVTs were more commonly observed in female dogs, dogs between 2-4 years of age, mixed breed, and without a chain. In females, TVTs were anatomically located in the vestibule vaginal area, while in males, they were found in the bulbous glands. Lower incidence of TVTs was observed in male dogs, age 0-2 years, with TVTs located in the vulvovaginal region in females and the penis in males. Chihuahua breed and breeder dogs also showed lower incidence of TVT. In conclusion, the results of this study suggest that both vincristine sulfate and vinblastine sulfate are effective treatment protocols for canine TVT in dogs.

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INTRODUCTION

The canine transmissible venereal tumor (TVT) is a contagious, round cell benign growth found in the external genitalia (penis and vulva) of dogs (Stockmann *et al*., 2011; Fathi *et al*., 2018). It is a sexually transmitted disease among dogs, also known as canine transmissible venereal granuloma, canine transmissible infectious sarcoma, sticker tumor, canine condyloma, infective

venereal tumor, or canine transmissible lymphosarcoma (Stimmelmayr, 2010). This tumor has also been observed in other canid species such as coyotes, jackals, wolves, and foxes (Das and Das, 2000). It is prevalent worldwide and considered endemic in over 90 countries (Strakova and Murchison, 2014). TVTs are primarily transmitted through sexual contact and social behaviors like sniffing, biting, scratching, and licking the infected areas (Kumar *et al*., 2014; Fathi *et al*., 2018). Both male and female dogs can be infected, with an incidence rate of 35.5% in males and 64.5% in females (Boscos and Ververidis, 2004). The occurrence is typically highest during the peak sexual activity, especially in female dogs during their estrus period. Dogs of any breed, age, or sex can be susceptible to this tumor (Park *et al*., 2006). TVTs are more prevalent in female dogs compared to male dogs due to their mating behavior. This is because many female dogs mate with a single infected male during their estrus period, whether they are in a confined household or roam freely (Rebbeck *et al*., 2009).

The clinical presentation of canine transmissible venereal tumor (cTVT) can vary among dogs depending on the location of the tumors. Infected dogs exhibit symptoms such as bloody preputial and vaginal discharges, genital swelling, reduced penile exposure, skin with ulcerative nodules, and a tendency to sniff the infected lesions (Kumar *et al*., 2017). The tumor site shows infiltration of plasma and lymphocyte cells, which contribute to tumor remission, necrosis, and cell apoptosis (Stimmelmayr, 2010). Treatment options for TVT include surgery, radiotherapy, and immunotherapy. However, the most effective method is chemotherapy, with vincristine being widely used, although reports of drug resistance have emerged (da Silva *et al*., 2012; Franco Andrade, 2012). The present study was conducted to examine and compare the effects of vincristine sulfate and vinblastine sulfate as chemotherapeutic agents against TVT in dogs. The study evaluated the hematological, cytological, and histopathological aspects of the dogs before treatment (day 0) and at 7, 14, 21, and 28 days after treatment.

MATERIALS AND METHODS

Experimental design

A total of twenty dogs, representing various breeds, both male and female, and ranging in age from 1 to 6 years, were included in this study. The dogs were presented at the Department of Theriogenology, University of Agriculture Faisalabad, Pakistan. The dogs underwent a thorough physical examination, complete blood count (CBC), biopsy, and cytology of the tumor to confirm the diagnosis before the administration of vincristine sulfate (CAS No: 2068-78-2; Sigma-Aldrich, Inc., USA) and vinblastine sulfate (CAS No: 865-21-4; ALB Technology Limited, Hong Kong) as chemotherapeutic agents.

One group (Group A) of 10 dogs received intravenous treatment of vincristine sulfate at a dosage of 0.025 mg/kg body weight once a week for five consecutive weeks, as described in a previous study by Tahira *et al*. (2013). On the other hand, Group B was treated with intravenous administration of vinblastine sulfate at a dosage of 0.1 mg/kg body weight once a week for a maximum duration of five weeks, following the protocol outlined in a study by Das and Das (2000).

Cytological and histopathological analysis of tumor

Blood samples, approximately 3 ml each, were collected at five different time points: 0, 7, 14, 21, and 28 days from the cephalic vein of each dog using disposable needles and EDTA-coated blood collection tubes for complete blood count (CBC) using an automatic blood analyzer (Mindray, Shenzhen, China). The blood analyses were conducted three times to ensure accuracy and reliability of the results.

Statistical analysis

A two-factor randomized factorial block design was employed to analyze the data, using GLM procedure within the ANOVA module in Minitab (Version 17.3.1; Minitab, Inc., Pine Hall Road, State College, PA, USA). The analysis assessed the effects of individual factors since the interaction between treatments and duration was found to be non-significant. To further differentiate between the means, Tukey's pairwise comparison test was employed. A p value of less than 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Effect on haemotological parameters

Table I shows the effects of vincristine sulfate and vinblastine sulfate on the hematological parameters of the dogs. There were no significant differences observed for RBC between vincristine sulfate and vinblastine sulfate, as well as among all the treatment days ($P>0.05$). WBC and lymphocyte profiles were significantly higher at day 0 (before treatment) compared to days 7 to 28 ($P<0.05$). The difference in WBC and lymphocyte profiles between vincristine sulfate and vinblastine sulfate was also significant, with vincristine sulfate showing higher levels ($P<0.05$). A decreasing trend was noted in platelet counts from day 0 to day 28, with a significant difference observed ($P<0.05$). Vincristine sulfate had significantly higher platelet counts compared to vinblastine sulfate ($P<0.05$).

Table I. Hematological parameters of dogs before (0 day) and after application (7, 14, 21, 28 days) of vincristine sulfate (n=10) and vinblastine sulfate (n =10).

Factors	Drug	Variables					
Duration (days)		RBC	WBC	Platelets	Lymphocyte	Monocytes	Granulocytes
0	Vincristine sulfate	5.43±0.35^{A}	23.26 ± 3.39^{A}	163.50 ± 12.23^{A}	24.76 ± 3.63^{A}	1.66 ± 0.34^{A}	0.40 ± 0.20^{AB}
7		5.56 ± 0.22^{A}	10.73 ± 1.66^{B}	119.60 ± 11.16^{B}	9.07 ± 1.53^{B}	0.81 ± 0.28^{C}	0.63 ± 0.38^{A}
14		5.44 ± 0.26^{A}	8.91 ± 1.44^{B}	104.20 ± 13.71^{C}	8.96 ± 1.55^{B}	1.07 ± 0.29^{AB}	0.58 ± 0.32^{A}
21		5.64 ± 0.25^{A}	12.08 ± 1.48^{B}	89.466 ± 10.73^{D}	11.38 ± 1.47^{B}	1.20 ± 0.28^{BC}	0.49 ± 0.30^{A}
28		6.05 ± 0.07^{A}	8.95 ± 1.14^{B}	67.250 ± 9.49^{E}	8.22 ± 1.10^{B}	0.75 ± 0.08^{C}	0.55 ± 0.22^{B}
0	Vinblastine sulfate	5.84 ± 0.40^{A}	16.92 ± 2.57^{A}	146.00 ± 14.24^{A}	26.13 ± 3.91^{A}	4.11 ± 1.12^{A}	0.82 ± 0.16^{AB}
7		5.65 ± 0.26^{A}	9.33 ± 1.46^{B}	111.40 ± 30.47^{B}	7.16 ± 1.62^{B}	1.36 ± 0.40^{C}	0.99 ± 0.16^{A}
14		6.51 ± 0.98^{A}	11.15 ± 0.92^{B}	90.20 ± 11.58^{C}	3.92 ± 1.28^{B}	3.07 ± 0.49^{AB}	0.78 ± 0.16^{A}
21		5.46 ± 0.21^{A}	7.81 ± 1.31^{B}	85.85 ± 21.03^{D}	3.2 ± 1.03^{B}	1.70 ± 0.33^{BC}	0.85 ± 0.26^{A}
28		5.10 ± 0.00^{A}	6.4 ± 0.00^{B}	56.33 ± 8.08^{E}	2.1 ± 0.00^{B}	0.60 ± 0.00^{C}	0.20 ± 0.1^{B}

Variables are shown with fitted mean values and standard error of the mean. Means with different superscripts in a column differed significantly ($P < 0.05$). RBC, red blood cells (1012/L); WBC, white blood cells (109/L); platelets (109/L); lymphocyte (109/L); monocytes (109/L); granulocytes (109/L).

Monocytes showed a significantly higher profile at day 0 compared to days 7, 21, and 28 ($P<0.05$), except for day 14 ($P>0.05$). Vinblastine sulfate had significantly higher monocyte levels compared to vincristine sulfate ($P<0.05$). Granulocyte profiles were significantly lower on day 28 compared to days 7, 14, and 21 ($P<0.05$). Vinblastine sulfate had significantly higher granulocyte levels compared to vincristine sulfate ($P<0.05$).

Effect on cytological and histopathological parameters

The cytological examination of the smear revealed the presence of round and polyhedral shaped cells. Upon staining with the Romanowsky stain, the cells appeared grayish in color, while staining with Eosin and hematoxylin resulted in a basophilic appearance (Fig. 1A). The cells exhibited variable numbers of nucleoli, typically basophilic in nature. Additionally, the presence of centrally located punctate vacuoles, which are considered the most distinctive cytological characteristic of CTV, were observed (Fig. 1B). The histological examination revealed the presence of a sheet of round individual cells with round vesicular nuclei. These cells were arranged in a branched shape and composed of fibrovascular and connective tissue networks (Fig. 1C). There was frequent infiltration of lymphocytes, macrophages, and red blood cells, with fewer plasma cells observed (Fig. 1D).

Among the dogs treated with vincristine sulfate, eight out of the ten dogs (80%) achieved complete recovery from day 14 onwards. The discharge from the external genitalia ceased within 3-6 days. However, two dogs experienced higher body temperature and paralysis. Biopsy conducted at 0 and 7 days after vincristine sulfate treatment revealed degenerative changes in the cells, including eosinophilic and vacuolated apoptotic cells in the cytoplasm, as well as condensed, irregular, fragmented, and lysed nuclei. Lymphocytes, both free and aggregated, infiltrated the tumor cells. Fibroblast proliferation, thickening of connective tissue septa, and blood vessel growth were also observed.

Among the dogs treated with vinblastine sulfate, nine out of the ten dogs (90%) achieved complete recovery from day 14 onwards. The discharge from the external genitalia ceased within 1-4 days, and no paralysis was observed during vinblastine sulfate treatment. Biopsy conducted at 0 and 7 days after vinblastine sulfate treatment showed similar observations to vincristine sulfate treatment, including changes in the cytoplasm and nuclei of tumor cells, loss of nucleoli, and the presence of fewer apoptotic cells as shown in Figure 2.

This study aimed to compare the impact of vincristine sulfate and vinblastine sulfate, both being chemotherapeutic agents, on TVTs in dogs. The assessment was conducted at different time points: day 0 (prior to treatment) and days 7, 14, 21, and 28 (post-treatment), focusing on hematology, cytological, and histopathological aspects.

According to previous studies (Nak *et al*., 2005; Lefebvre *et al*., 2007), vincristine treatment has been associated with lower WBC, RBC, and platelet count. On the other hand, vinblastine treatment has been reported to potentially cause anemia and leucopenia between days

4 and 10, with recovery depending on the administered dose (McEvoy, 2007). However, in the current study, we did not find any significant effect of the treatments on the RBC profile at different durations. Additionally, both treatments did not have a significant influence on RBCs, although mean values remained within an acceptable range. This indicates that both chemotherapeutic agents played a contributory role in maintaining RBC levels and improving immune response.

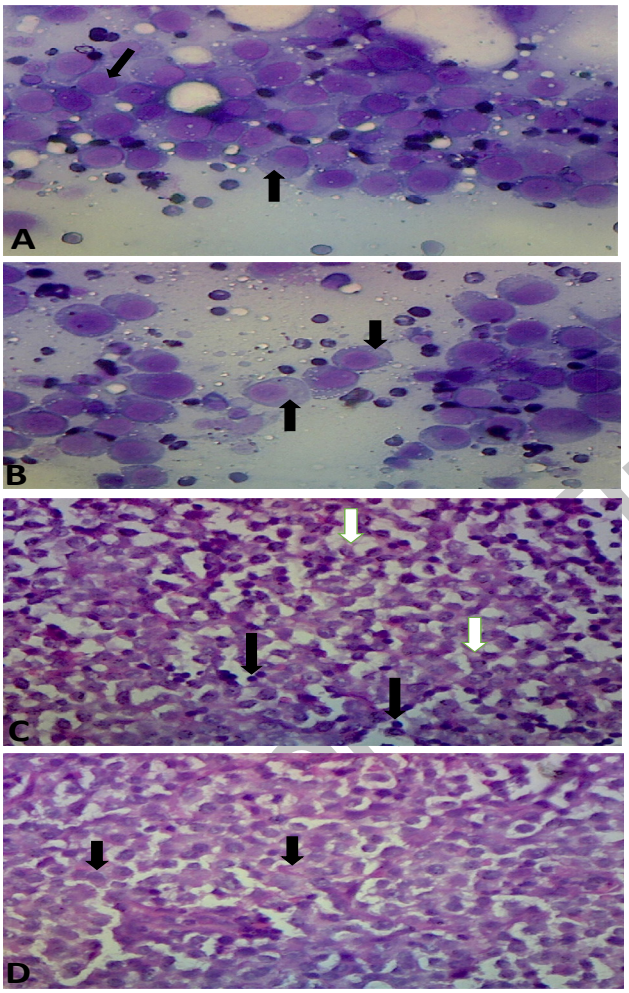

Fig. 1. Smear of TVT cells showing greyish TVT cells (A), Pleomorphic round cells (B), Connective tissue (white arrow) and RBC (black arrows) in C and lymphocytes (D). Magnification: X400.

In the present study, the profiles of WBCs and lymphocytes were significantly higher at day 0 but remained similar afterward. Vincristine sulfate showed significantly higher WBC, platelet, and lymphocyte profiles compared to vinblastine sulfate. We observed a

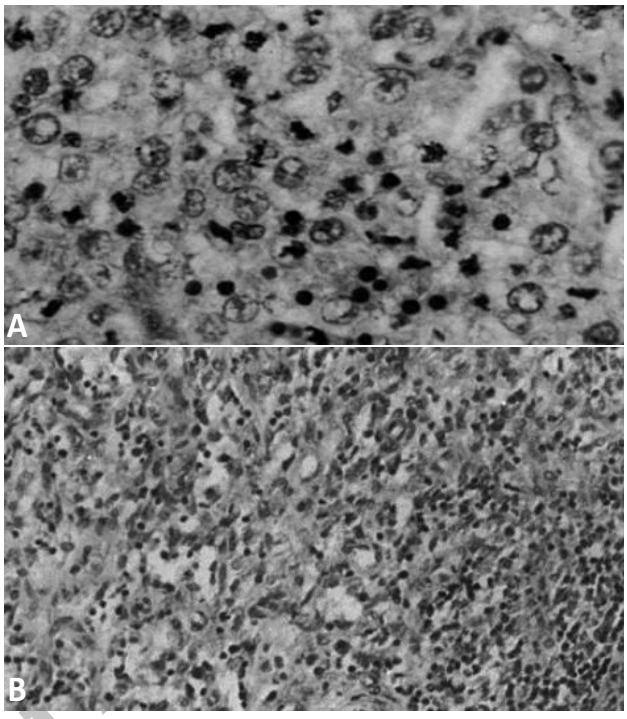

Fig. 2. Effect of vincristine (A) and vinblastine (B) treatment after 7 days. Magnification X400. 124 × 74 mm (96 x 96 DPI). Cytological examination revealed round to slightly polyhedral cells with grayish cytoplasmic appearance upon staining. Histopathological examination confirmed the presence of individual round cells with vesicular nuclei in TVTs.

significantly decreasing trend in platelets from day 0 to 28 post-treatment. However, in contrast, a study involving a single Dalmatian female with TVT treated with vincristine at 0, 1, 2, 3, and 4th week showed an increasing trend in platelets and lymphocytes, which may affect the overall significance of our results (Varughese *et al.*, 2012). Another study in rats using vinblastine (0.1, 0.2, 0.4, 0.8 mg/kg) and vincristine (0.1, 0.2, 0.4, 0.8 mg/kg) reported a decrease in leucocyte and platelet count after administering these drugs for a week (Chandorkar, 1973; Zubair *et al.*, 2020). Regarding monocytes and granulocytes, we observed significantly higher profiles of monocytes at day 0 compared to days 7, 21, and 28, except for day 14. Granulocytes had a significantly lower profile on day 28 compared to days 7, 14, and 21. However, vinblastine sulfate showed significantly higher levels of monocytes and granulocytes compared to vincristine sulfate. In contrast to our results, Kumar *et al.* (2017) found an average concentration of monocytes in healthy (2±0.36) and affected (2.02±0.22) dogs treated with vincristine sulfate, suggesting that vinblastine treatment has improved

by sustaining the overall levels of monocytes. Overall, our findings indicate that vincristine sulfate and vinblastine sulfate have different effects on hematological parameters. Vincristine sulfate tends to result in higher WBC, platelet, and lymphocyte profiles, while vinblastine sulfate appears to have a more significant impact on monocytes and granulocytes. These differences in the hematological effects of the two chemotherapeutic agents may have implications for their clinical use in the treatment of transmissible venereal tumors in dogs.

Cytology is considered a rapid, cost-effective, and accurate method in comparison to histopathological examination (Florez *et al*., 2012). In cytological examination, we observed round and polyhedral shaped cells with varying numbers of nucleoli. Additionally, we identified centrally located punctate vacuoles, which are considered the most distinctive cytological characteristics of canine TVTs.

During histological examination, we observed a sheet of round individual cells with round vesicular nuclei. These cells were arranged in a branched shape and composed of fibrovascular and connective tissue networks. There was a frequent infiltration of lymphocytes, macrophages, and red blood cells, while fewer plasma cells were present. The dogs showed recovery within 14 days following the application of both treatments. The discharge from the external genitalia ceased after 3-6 days with vincristine and 1-4 days with vinblastine. After 0 and 7 days of biopsy, similar observations were made for both treatments. Degenerative changes were observed in the cytoplasm, characterized by eosinophilic, vacuolated apoptotic cells. Similarly, degenerative changes were observed in the nuclei, including condensed, irregular, fragmented, and lysed cells. Lymphocytes, both free and aggregated, were observed infiltrating the tumor cells. Fibroblasts appeared to increase, connective tissue septa thickened, and blood vessel growth was observed. Vinblastine treatment showed fewer apoptotic cells and fewer lymphocyte infiltrations compared to vincristine treatment. These findings indicate that both treatments potentially controlled the localized antibody-mediated program of TVT, improved overall development, and regressed the influence of TVTs (Mascarenhas *et al*., 2014). The anti-cancer capabilities of vincristine and vinblastine are associated with their inhibition of cell division at the onset of mitosis. This occurs when the development of microtubules is interrupted, thereby affecting cell division and resulting in apoptosis. Vincristine also acts as a potential inhibitor of protein synthesis of DNA and RNA (Chu and DeVita, 2015). P-glycoprotein (P-gp), a transporter protein encoded by the MDR1 gene, is present in normal tissues as well as tumor tissues and offers multidrug resistance. It acts as an efflux pump for various molecules, including vincristine, vinblastine, doxorubicin, avermectins, and loperamide (Mealey *et al*., 2003; Korystov *et al*., 2004). While the mechanism of P-gp is not fully understood, it has been reported to efflux substances out of cells, contributing to drug resistance (Dowling, 2006). A study suggests that vinblastine/vincristine may induce the overexpression of P-gp (Arora and Shukla, 2003). Interestingly, vincristine and vinblastine have different mechanisms of cytotoxicity and antitumor spectrum, and they do not show cross-resistance in tumors where both are active (Armstrong, 1968; Carlson, 1969). However, both drugs may share a common thrombocytosis-promoting effect beyond their oncolytic action (Chandorkar, 1973).

These findings suggest that the application of vincristine sulfate and vinblastine sulfate as chemotherapeutics improved the regression of TVTs in dogs. In future research, we aim to explore the possibility of a synergistic effect between vincristine and vinblastine against TVTs and other tumors in dogs and cats by using appropriate dose concentrations. This approach could have a beneficial impact on the disease and potentially lead to advancements in chemotherapy practices.

CONCLUSION

In conclusion, this study demonstrated a significant association between lymphocyte count and treatment duration, as well as a significant effect of treatment duration on platelet and white blood cell concentrations for both vincristine sulfate and vinblastine sulfate. Cytological examination revealed distinct cellular characteristics, while histopathological examination confirmed the presence of TVTs. The study also identified specific demographic and anatomical patterns associated with TVTs in dogs. Overall, the findings support the efficacy of vincristine sulfate and vinblastine sulfate as effective treatment protocols for canine transmissible venereal tumors (TVTs).

DECLARATIONS

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IRB approval

All of the experimental procedures applied in this study were conducted according to the principles of The University of Agriculture, Faisalabad, Pakistan Animal Care and Use Committee, which approved the study protocols.

Ethical approval

This study was approved by the Departmental Committee on Animal Ethics and Welfare, University of Agriculture Faisalabad, Pakistan.

Statement of conflict of interest

The authors have declared no conflict of interest.

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