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Studies on transmissible venereal tumour (TVT) in canines

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Abstract
The Canine Transmissible Venereal Tumour (TVT) is a specific neoplastic tumour commonly found in canines. It is usually malignant and transplantable tumour most often spread through sexual intercourse, by living cancer cells. Which mainly affects external genitalia of the male and female dogs. CTVT case was diagnosed based on the gross lesions, anatomical location, cytology and impression smears of the tumour were done. Tumour cytology showed cytoplasm of the cells was blue in colour with many clear distinct cytoplasmic vacuoles. In the present study, Group I dogs were administered with 1 ml of normal saline as control group considered to establish normal values. Group II dogs were treated with Injection Vincristine @ 0.5 mg/m2 or 0.025 mg/kg b.wt administered I/V once in a week for 4 to 6 weeks. Appreciable tumour regression was noticed within four to six weeks. Four dogs (66.66%) showed complete cure by the fourth dose itself. Dogs receiving Vincristine sulphate develops anaemia and leukopenia, animals showed vomiting and diarrhoea. In some, drug resistance was noticed leading to delay in the reduction of tumour mass and to combat the problem of drug resistance Ivermectin an antineoplastic agent was used along with Vincristine. Group III dogs were treated with Vincristine @0.025 mg/kg b.wt once in a week and Ivermectin 500 mcg per kg body weight S/C at 2 weeks Interval. 5 dogs showed (83.33%) complete clinical regression of the tumour just after 2 weeks of chemotherapy, Number of treatment cycles required for complete disappearance of the tumour was less. In some CTVT cases drug resistance was noticed leading to delay in reduction of tumour masses, to combat problem of drug resistance Ivermectin an antineoplastic agent was used along with Vincristine. Group IV were treated with Vincristine @0.025 mg/kg b.wt and Ivermectin 200 mcg per kg b.wt S/C at 2 weeks interval animals showed clinical improvement after 3week of chemotherapy after one dose of vincristine. Side effects like vomiting and alopecia were observed in 3 animals after 2nd dose.

Keywords: Canine transmissible venereal tumour, incidence, cytology, vincristine, ivermectin

Introduction
Tumour is an excessive and uncoordinated proliferation of cells with no useful function. Canine Transmissible Venereal Tumour (CTVT) is a common cause of death in dogs. This tumour is usually seen in young sexually mature stray dogs with uncontrolled reproductive activity involving external genitalia. Synonyms of Canine transmissible venereal tumour (CTVT) are Sticker's sarcoma, Sticker tumour, transmissible venereal tumour (TVT), contagious venereal tumour, transmissible lymphosarcoma, transmissible venereal sarcoma, venereal granuloma, infectious granuloma, canine condyloma, infectious sarcoma and contagious lymphosarcoma. Usually, the tumour mass resembles a cauliflower, is friable, and ranges in colour from red to flesh. This condition results in pain, haemorrhages and serosanguineous discharges from the external genitalia in dogs. Both male and female dogs aged 2 to 5 years are more likely to get the tumour. During breeding among infected animals, the disease is horizontally transmissible from male to female and vice versa. In females, the vaginal area is affected, whereas in male's penis and prepuce are affected with benign reticuloendothelial tumour of the dogs.

Material and Methods
For present study, 18 Dogs of different breeds, ages and both sexes which were presented to the Teaching Veterinary Clinical Complex with a history of bleeding from genital region, tumour like growth in the external genitalia were screened for this study. A case of TVT was diagnosed based on the gross lesion, anatomical location. Cytology and impression smears of the tumour was done for confirmatory diagnosis of CTVT. Dogs were screened for signs such as the presence or absence of bleeding from the external genitalia, licking behaviour,

cauliflower-like mass in genitalia region, difficulty in urination, presence or absence of foul odour and bulging of perineal region. The tumours were examined for its shape, size, location and presence of bleeding associated with them. Other systemic effects were also recorded in affected dogs.

Impression smear and cytology

1. Cytology was obtained as per technique described by Antonov (2017) [3] The female animal was restrained in standing position, cells were collected by using saline moistened cotton swab. In female dogs the sterile cotton swab was passed in the dorsal commissure of vulva, then swab was rotated through complete revolution in clock wise or anti clock wise and withdrawn subsequently.
2. The tumour mass protruding from vulva was washed with normal saline to remove any debris or faecal matter sticking to the mass.
3. Impression smears were taken by moderately pressing microscopic slides over the lesions for cytological examination.
4. The male dogs were restrained in left or right lateral recumbency and the prepuce was retracted in order to exteriorize penis up to the level of the bulbus glandis as well as the partial part of the prepuce. Impression smears were collected from different areas of tumour mass. The impression smear was obtained following the same procedure as that of the female dogs.

Theraputic trails: Total of 24 dogs of either sex of TVT cases were randomly allotted in to following therapeutic groups.

Group I: Control Six healthy dogs were administered with 1ml of Normal saline solution (NSS) which served as control

Group II: Vincristine Sulphate The animals in this group received vincristine sulphate at the dose rate of 0.025 mg/kg body weight diluted in 10 ml normal saline solution injected intravenously as slow infusion drip. Treatment was repeated weekly interval until the complete disappearance of the clinical evidence of the tumour.

Group III: Vincristine and Ivermectin combination (Vincristine @ 0.025 mg/kg body weight and Ivermectin 500 mcg/kg body weight) In this group all dogs were treated with Vincristine sulphate @ 0.025 mg/kg weekly interval and Ivermectin @ 500 mcg/kg body weight subcutaneously once in 2 weeks until the complete disappearance of the tumour. Before subjecting the animal to chemotherapy, the blood sample was collected to study haematological and biochemical parameters.

Group IV: Vincristine and Ivermectin combination (Vincristine @ 0.025 mg/kg body weight and Ivermectin 200 mcg/kg body weight) In this group all dogs were treated with Vincristine sulphate @ 0.025 mg/kg weekly interval and Ivermectin @ 200 mcg/kg body weight subcutaneously once in 2 weeks until the complete disappearance of the tumour. Before subjecting the animal to chemotherapy, the blood sample was collected to study haematological and biochemical parameters.

Results and Discussion

Retrospective study of CTVT

The pursual of recorded data revealed that, the dogs presented to the Veterinary Clinical Complex for diagnosis and treatment of various reproductive tract disorders during the period from March 2015 to 31st March 2021 were about 10798 cases. Out of which 1381 cases were TVT positive, then the incidence of TVT was approximated to 12.78%. it is partially in accordance with Chikweto *et al*. (2013) [7] who reported an incidence rate of 18% in Grenada, West Indies retrospectively involving 420 tumour cases. Other authors Gondotra *et al*. (1993); Purohit (2009) [20] and Das *et al*. (2020) [9] reported a high occurrence of TVT within a range of 23-43%, due to uncontrolled sexual behaviour of large stray dog population.

Breed wise Incidence: The incidence of TVT affected dog breeds were Mongrel (23.38%), Labrador Retriever (16.65%), German Shepherd (13.32%) followed by other breeds, such as Pomeranian (9.99%), Cross breed (9.99%), Spitz (6.7%), Dachshund (6.71%), Doberman (3.33%), Great Dane (3.33%), Golden Retriever (3.33) and Dalmatian (3.33%) The high incidence found in Mongrel retrospectively. The increased incidence in the mongrel dogs is probably due to the large population of free roaming stray dogs and uncontrolled sexual behaviour.

Sex: In the present study, the occurrence of TVT in dogs revealed an incidence of 55.56% in female dogs and 44.44 % in males. This incidence percentage was in agreement with Boscoss and Ververdis (2004) [5], who reported that females were affected more than males at 64.5% and 35.5% respectively. Nak *et al*. (2005) [19] reported 76% and 23% in females and males, respectively. Females were more susceptible and more commonly infected than males because one infected male often mates with numerous females.

Clinic sings: All the animals were presented with the complaint of bleeding from the external genitalia for the past fifteen days to one month. Other clinical signs exhibited by the animals affected with CTVT included excessive licking of external genitalia, perineal bulging, ulceration of the tumour, dysuria, deformation of external genitalia, mating refusal, anorexia, weakness and weight loss. These findings were in agreement with previous reports of Boscos and Ververdis (2004) [5]; Tella *et al*. (2004) [22]; Nak *et al*. (2005) [19] and Purohit (2009) [20].

Location of the Tumour: Among 10 female dogs with CTVT two bitches showed growth on vulval lips, 6 bitches showed tumour mass in the posterior vagina, 2 bitch showed tumour mass at the vulvo vestibular junction and in case of male dogs the tumour mass was located at the caudal part of the penis, tip of penis and at preputial cavity and mucus membrane. This is in agreement with Boscos and Ververidis (2004) [5]; Das and Das (2000); Eze *et al*. (2007) while, Ganguly *et al*. (2016) reported neoplastic lesions located at vestibule and vagina in female dogs and at caudal part of penis (bulbus glandis) in male dogs.

Cytological changes: In the present study, cytology smear revealed presence of degenerative neutrophils, oval to round shape nucleus, one or two prominent nucleoli, clear cytoplasmic vacuoles with basophilic cytoplasm. Major changes in regressing tumour cytology were loss of cellular characters and formation of cytoplasmic vacuoles. The present study is in agreement with Thangathurai *et al*. (2008);

Purohit (2009) [20] and Tella *et al*. (2004) [22] who observed similar prominent cytological features of the presence of clear cytoplasmic vacuoles in TVT affected dogs. There is a lower nuclear to cytoplasmic ratio with distinct cytoplasmic vacuoles that can be helpful in distinguishing this tumour from lymphomas, plasmacytoma., or histiocytoma.

Treatment and response to therapy: Among the dogs affected with TVT, male and female dogs were selected at random and divided into three groups each consisting of a minimum of six animals and the efficacy of different treatment regimens were evaluated.

Group I: Six healthy dogs were administered with 1 ml of Normal saline as the control group considered to establish normal values. The animals in the control group remained healthy throughout the experimental period.

Group II

Clinical Response to Treatment trail

Six dogs of this group were treated with Injection Vincristine @ 0.5 mg/m2 or 0.025 mg/kg body weight mixed with Normal saline and administered IV once in a week for 4 to 6 weeks. Appreciable tumour regression was noticed within four to six weeks. Present findings are in agreement with Athar *et al*. (2001) [4]; Boscos and Veveridis (2004) [5]; Said *et al*. (2009) [21]; Da Silva *et al*. (2014) [8]; Purohit (2009) [20] who treated with Vincristine as a single agent administered weekly once for 4 to 6 weeks yields cure for TVT.

Side effects Dogs that received Vincristine sulphate developed anaemia and leukopenia, 2 animals showed vomiting and diarrhoea. Some dogs showed depression, dullness, and alopecia, and extravasation of the drug during intravenous administration resulted in development of necrotic lesions. The present study is in agreement with Leigh *et al*. (2008) [16]; Gandotra *et al*. (1993) [12, 13] and Martins *et al*. (2005) [18] who opined that Vincristine sulphate was found to be effective against TVT. However, side effects such as anorexia and vomiting were observed, extravasation of the drug during intravenous administration resulted in development of necrotic lesions, which could be managed by palliative drug therapy.

Group III

Clinical Response to Treatment trail

Six dogs in this group were treated with vincristine @ 0.025 mg/kg b.wt once in a week and Ivermectin 500 mcg per kg b.wt S/C at 2 weeks Interval. Complete clinical regression of the tumour just after 2 weeks of chemotherapy was noticed. Number of cycles of treatment required for complete disappearance of the tumour was less. 3 animals showed side effects like dullness reduced food intake, vomiting and alopecia were observed. Present study excellent clinical response in dogs treated with vincristine @ 0.025 mg/kg b.wt once in a week and Ivermectin 500 mcg per kg b.wt S/C at 2 weeks Interval.

Side effects Vincristine combined with ivermectin might result in more intense adverse reactions in dogs with TVT particularly in those with poor clinical status this however did not occur in this study. Side effects such as anorexia and vomiting were observed in one case after 1st dose of injection and mild leukopenia was noticed. Present study is in agreement with Bulhosa *et al*. (2020) [6].

Group IV

Clinical Response to Treatment trail

Six dogs in this group were treated with vincristine @0.025 mg/kg b.wt and Ivermectin 200mcg per kg body weight S/C at 2 weeks Interval. one dog in which the disease was in very early stage complete clinical cure after 2 weeks of chemotherapy was noticed and nodule like lesion was present on the vulval floor. Other dogs showed clinical improvement after 3week of chemotherapy and reduction in vaginal bleeding observed after one dose of vincristine. Side effects like vomiting and alopecia were observed in 3 dogs after 2nd dose. Similar results were observed by Lapa *et al*. (2012) [15]; Lopes *et al*. (2015) [17] and Abeka (2019) [1] who reported the synergistic effect of combination of vincristine and ivermectin that may increase the antitumour effect and reduce the resistance to vincristine.

Side effects Side effects such as anorexia and vomiting were observed in one case after 2nd dose of injection also mild leukopenia was noticed. In the present study, combination of vincristine plus ivermectin on different days exhibit reduced food intake, nausea tumour mass has reduced within 2 weeks in 5 animals. Similar results were reported by Andrade *et al*. (2009) [2] and Lapa *et al*. (2012) [15]. This early reduction of tumour mass is due to the noticed through cytology.

Conclusion

With the result of the present study, it is concluded that combination of Injection Vincristine and ivermectin has shown faster response in dogs with lower severity of chemotherapeutic side effects whereas, vincristine was potent in the treatment of CTVT which showed complete regression of tumours but the therapeutic effect was a bit delayed and the side effects were more. However, combination of Vincristine and Ivermectin were found more advantages and faster in response to vincristine alone

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