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Research Article

COMPARATIVE CARDIOTOXIC EFFECTS OF VINCRISTINE AND DOXORUBICIN IN CANINE CHEMOTHERAPY

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ABSTRACT

This study aimed to compare the cardiotoxic effects of vincristine and doxorubicin in the clinical cases of dogs undergoing chemotherapy. Twelve dogs with soft tissue tumours were divided equally into two groups at random. Vincristine sulphate was administered weekly to group-1 at dose rate 0.025mg/kg body weight. In group-2, doxorubicin hydrochloride was administered at weekly intervals at a dose rate of 1mg/kg body weight. Blood samples were collected at regular intervals for analysis of ghrelin and cardiac troponin I (cTnI). Echocardiography was also performed to evaluate the left ventricular cardiac functions namely, (ejection fraction) EF, (fractional shortening of the left ventricular diameter) FS and (peak early to late diastolic mitral inflow velocity ratio) E/A ratio. In group 1, no significant changes in ghrelin, cTnI, EF, FS and E/A ratio were observed, but substantial changes were observed in all of these in group 2. This demonstrates that doxorubicin is more cardiotoxic than vincristine.

Keywords: Chemotherapy, Dogs, Doxorubicin, Vincristine

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Dogs are not only considered as companion animals but also treated as the family members from a long time (Stephens, 2019). They suffer from many diseases but tumors are a major cause of mortality in them (Dias-Pereira, 2022). Surgery is the preferred method for treating tumours and chemotherapy is used as an adjunct to reduce the chances of recurrence and control the metastasis (Sarver *et al.*, 2022). A wide variety of chemotherapy agents such as mitoxantrone, vincristine, cyclophosphamide, doxorubicin, methotrexate etc. are used in treating tumours. The cardiotoxic effects shown by these drugs must be taken care of and should be diagnosed as early as possible. Cardiac troponin I (cTnI) is found to be very specific and sensitive marker of myocardial injury (Langhorn and Willesen, 2016) and its increased concentration precedes the development of cardiac dysfunction (Gallay-Lepoutre *et al.*, 2016). Ghrelin directly acts on cardiovascular cells to protect the heart from diseases like cardiac arrest, myocardial infarction, pulmonary hypertension and cardiac arrhythmias (Hosoda, 2022). Apart from hormone estimation, echocardiography serves as a very efficient tool in assessment of heart condition (Keller *et al.*, 2023). It can be used to assess diastolic functioning of left ventricle by evaluating mitral inflow velocity profile by measuring peak values of early (E) and late (A) diastolic velocities and determination of the ratio between them (E/A ratio) (Gallay-Lepoutre *et al.*, 2016) using M-mode measurements. The fractional shortening of left ventricular diameter can be evaluated to check cardiomyopathy (Surachetpong, 2016). The deviation of these measurements from normal can be an indicator of cardiac abnormalities and can also serve to assess the drug induced cardiotoxicity (Hernandez-Suarez and Lopez-Candales, 2017).

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MATERIAL AND METHODS

This research was performed in clinical cases of twelve dogs having soft tissue tumours (transmissible venereal tumour, mammary tumour, papilloma etc.) which were presented at Veterinary Clinical Complex in the College of Veterinary Sciences, LUVAS, Hisar. The animals regardless of age, breed, or sex, were split into two groups of six each at random. Tumours were excised surgically and respective samples were processed for histopathological examination. Afterwards, the animals in group-1 received intravenous vincristine sulphate treatment at a dose rate of 0.025 mg/kg body weight (Prabha *et al.*, 2019), whereas the animals in the group-2 received intravenous doxorubicin hydrochloride treatment at a dose rate of 1 mg/kg body weight (Phogat, 2015). Both the agents were diluted in 100 ml of 0.9% normal saline solution and slowly given in saphenous or cephalic vein intravenously over the course of 10-15 minutes at weekly intervals commencing on day 0, 7th, 14th and 21st. Blood collection for analysis was done at 0, 7th, 14th, 21st day before chemotherapy and final sampling was done on 28th day to observe the effects of last chemotherapy dose.

Blood was collected in EDTA vials for ghrelin estimation and in serum vials for cTnI estimation by ELISA method. Before chemotherapy, trans-thoracic echocardiography was done in both right and left lateral recumbency at the level of 3rd to 4th intercostal space to assess left ventricular functions namely EF, FS and E/A ratio. The paired t-test was used for the statistical analysis of the data within the group. The t-test was used to statistically

Table 1. Table showing the breed, age, sex and type of soft tissue tumour in group-1 and 2

Groups	Dog				Type of soft tissue tumour	Malignancy
	Sr. no.	Breed	Age	Sex		
Group 1	1	Labrador	12 yrs	F	Mammary tumour	Malignant
	2	Cross bred	12.5 yrs	F	Mammary tumour	Malignant
	3	Labrador	13 yrs	F	Mammary tumour	Malignant
	4	German Shepherd	6 yrs	M	Oral tumour	Benign
	5	Lhasa Apso	12 yrs	F	Mammary tumour	Malignant
	6	Cross bred	7 months	M	Papilloma	Benign
Group 2	1	German Shepherd	11 yrs	F	Mammary tumour	Malignant
	2	Pit Bull	3 yrs	F	Mammary tumour	Malignant
	3	Rottweiler	6 yrs	M	Oral tumour	Benign
	4	Great Dane	7 yrs	F	Mammary tumour	Malignant
	5	German Shepherd	6.5 yrs	M	Oral tumour	Benign
	6	Cross bred	10 yrs	F	Mammary tumour	Malignant

Table 2. Comparison of the Impact of Vincristine Sulphate (V) and Doxorubicin Hydrochloride (D) on Cardiac Parameters in Groups-1 and 2. The mean values are reported along with their respective standard errors (±)

Parameters (Units)	Drug	0 day	7day	14 day	21 day	28 day	Normal value
Ghrelin (ng/ml)	V	1.90+0.54	1.72+0.50	2.02+0.45	2.16+0.43	1.93+0.47	1.20-1.80
	D	1.02^{a}+0.23	1.31^{ab}+0.37	1.45^{b}+0.41	1.33^{c}+0.30	1.47^{bc}+0.31	
cTnI(pg/ml)	V	69.64^{A}+3.79	70.53^{A}+3.16	74.23^{A}+1.63	75.33^{A}+3.00	73.76^{A}+3.68	20.00-70.00
	D	125.91^{aB}+9.45	495.21^{bB}+40.11	958.33^{cB}+166.65	1088.41^{dB}+136.86	1203.63^{eB}+129.62	
EF(%)	V	62.39+1.54	63.51+1.68	62.71+1.91	64.12+1.66	62.62+2.09	50.00-65.00
	D	65.09^{a}+2.82	63.75^{b}+2.86	62.56^{c}+2.79	61.01^{d}+2.82	59.27^{e}+2.88	
FS(%)	V	29.42+0.83	31.03+1.08	31.29+1.35	30.62+0.90	29.83+1.31	25.00-30.00
	D	31.36^{a}+1.51	30.49^{b}+1.45	29.41^{c}+1.52	29.03^{bc}+1.47	27.95^{d}+1.28	
E/ARatio	V	1.50+0.04	1.44+0.07	1.48+0.06	1.44+0.04	1.46+0.06	1.30-1.60
	D	1.55^{a}+0.04	1.50^{ab}+0.05	1.44^{b}+0.04	1.40^{ab}+0.05	1.33^{c}+0.03	

In a row, superscript (a, b, c, d) differ significantly at $p<0.05$; In a column, superscript (A, B) differ significantly at $p<0.05$

analyze the data between the groups. Table 1 shows the breed, age, sex and type of soft tissue tumour in group-1 and 2.

RESULTS AND DISCUSSION

Comparison of the effects of vincristine sulphate and doxorubicin hydrochloride on cardiac parameters namely ghrelin, cardiac troponin I, EF, FS and E/A ratio were assessed and the results are shown in Table 2.

Ghrelin showed no significant change in group-1 while it significantly increased in group-2 upto 28th day except at day 21. Ghrelin acts as orexigenic hormone (Ibrahim Abdalla, 2015) and also it is cardioprotective (Mao *et al.*, 2014). The significantly increased levels of ghrelin in group-2 might be due to cardiac injury and inappetence which triggers increase in ghrelin production. There was a non-significant increase in the cTnI levels in group-1 and significant increase in group-2 throughout the course of study. The increase in cTnI value was very high in group-2 as compared to group-1. cTnI is an excellent indicator of injury to the myocardium and the damage to myocardium is directly in proportion to the cTnI release (Aydin *et al.*, 2019). EF showed no significant changes in group-1 in EF while in group-2, EF decreased significantly upto day 28. In group-1, non-significant increase was observed in the FS at 7, 14, 21 and 28 while in group-2, FS was observed to be reduced at day 7, 14, 21 and 28 as compared to the base value. In group-1, non-significant decrease was observed in E/A ratio while significant decrease was observed in group-2 up to day 28. There was a significant decrease in the echocardiographic parameters i.e. EF, FS and E/A ratio in group-2 which could be due to cardiomyopathy. Changes in diastolic functions have also been reported earlier in patients treated with doxorubicin and evaluation of mitral inflow velocity profile (E/A ratio) helps in assessing diastolic dysfunction (Gallay-Lepoutre *et al.*, 2016; Hallman *et al.*, 2019). Evaluation of left ventricular ejection fraction and fractional shortening also indicate cardiomyopathy (Piper and McDonagh, 2015). The current study suggests that doxorubicin is more cardiotoxic than vincristine; however, due to heterogenous experimental animal population, more cases need to be

analysed in future for a better understanding.

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