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Comparative study of haemato-biochemical effects of vincristine and doxorubicin in chemotherapy of dogs

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Abstract
The study was undertaken to evaluate the comparative effects of vincristine and doxorubicin on haemato-biochemical parameters. For this, twelve animals having soft tissue tumours were randomly divided in two groups of six animals each. In group I, chemotherapy with vincristine sulphate at the dose rate of 0.025mg/kg body weight was given at weekly intervals. In group II, chemotherapy with doxorubicin hydrochloride at the dose rate of 1mg/kg body weight was done at weekly intervals. Blood samples were taken before chemotherapy for haemato-biochemical analysis. It was found that both vincristine and doxorubicin cause bone marrow suppression leading to leucocytopenia and neutropenia. Thrombocytosis was found in group I while thrombocytopenia was found in group II. Increase in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), triglycerides, alkaline phosphatase (ALP), cholesterol, gamma-glutamyl transferase (GGT), blood urea nitrogen (BUN), creatinine, lactate dehydrogenase (LDH) and creatine kinase (CK) was found in both groups. This shows that both drugs cause hepatotoxicity, nephrotoxicity and cytotoxicity.

Keywords: Chemotherapy, dogs, doxorubicin, vincristine

1. Introduction
Tumours are a major cause of mortality in dogs and the incidence of tumours in dogs is reported to be around 35-40% [1]. Todorova *et al.* [2] stated that out of the major modes of treatment (i.e. surgery, chemotherapy and radiotherapy), only chemotherapy is known to be helpful in controlling systemic or metastatic tumours. Various chemotherapeutic drugs like vincristine, doxorubicin, mitoxantrone, methotrexate, cyclophosphamide etc. are used to treat tumours. Vincristine is one of the most commonly used chemotherapeutic drug to treat various neoplasms like leukemia, lymphoma and sarcomas in dogs and cats [3]. Doxorubicin is an anthracycline antibiotic and used as antitumour agent. Adverse effects of vincristine include gastrointestinal alterations, extravasation injury and myelosuppression [4]. Similarly, doxorubicin can cause hair loss, rashes, bone marrow suppression, gastrointestinal disturbances, anaphylaxis, tissue damage at the site of injection and treatment-related leukaemia. There are various hematological and biochemical parameters which can be assessed regularly to determine the detrimental effects of the drug during the course of chemotherapy.

2. Materials and Methods
The present study was conducted on twelve clinical cases of dogs with soft tissue tumour and brought to Veterinary Clinical Complex, College of Veterinary Sciences, LUVAS, Hisar. The animals were divided randomly in two groups of six animals each irrespective of age, breed and sex. The animals of first group were treated with vincristine sulphate at the dose rate of 0.025 mg/kg body weight intravenously and the animals of second group were treated with doxorubicin hydrochloride at the dose rate of 1 mg/kg body weight intravenously. Both the drugs were given weekly at 0, 7, 14 and 21 day after dilution in 100 ml of 0.9% normal saline solution slow intravenously in cephalic or saphenous vein over a period of 10-15 minutes. Blood sampling was done at 0, 7, 14, 21 and 28 day before chemotherapy.
Blood samples were collected in EDTA, 3.8 % NaF (for glucose estimation) and serum vials. Haematological parameters were assessed using the auto-analyzer machine (Haematology Cell Counter MS4s, France) at the Department of Veterinary Clinical Complex. Biochemical parameters were analysed with EM 200™ analyzer using commercially available Transasia XL system pack kits procured from M/S Transasia Biomedical Limited, Mumbai. Sodium and

potassium were analysed by flame photometer machine. Cortisol was estimated in serum by ELISA method.

To evaluate the comparative haemato-biochemical effects of vincristine and doxorubicin, following parameters were investigated at above mentioned time intervals. The haematological parameters were haemoglobin (Hb), packed cell volume (PCV), total leukocyte count (TLC), differential leukocyte count (DLC), total platelet count (Thrombocytes). The biochemical parameters included glucose, triglycerides, total cholesterol, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), direct bilirubin, blood urea nitrogen (BUN), creatinine, total plasma proteins, albumin, globulin, albumin: globulin ratio (A:G ratio), sodium, potassium, calcium, magnesium, chloride, cortisol. The statistical analysis of data within the group was done by paired t-test. Data between the groups was statistically analysed by t-test.

3. Results and Discussion

The haematological results obtained are shown in Table 1 and the biochemical results are shown in Table 2. There was a significant decline in the Hb at 7th day in both the groups and then an increase in Hb at 28th day was observed. The fall in Hb was due to the blood loss during surgery and due to the bone marrow suppressing effect of the chemotherapeutic drugs [5].

The TLC showed a significant decline in both the groups from day 0 to day 28. There was a sharp decline in TLC at day 7 which could be due to cumulative effects of administration of chemotherapeutic drug and the antibiotics after surgery. The cytotoxic drugs suppress the multiplying precursor cells of the bone marrow and decreases production of the leucocytes [6]. Significant neutropaenia was observed in group I upto 28th day while no significant changes were observed in group II. Similar results were obtained by Yadav *et al.* [7] after chemotherapy with doxorubicin in dogs with TVT. Significant thrombocytosis was observed in group I upto day 28th while significant thrombocytopenia was observed in group II upto day 28th of the study. This could be due to the acceleration of breakdown of megakaryocytes and stimulation of thrombopoiesis by vincristine [8]. Thrombocytopenia in group II could be due to bone marrow suppression and was also observed by Yadav *et al.* [7]

No significant change in PCV was found in group I but small yet significant decrease in PCV was found in group II. The decrease could be due to bone marrow suppression by the chemotherapy. But this decreased PCV was within the normal PCV range in dogs i.e. 36-60 % [9].

Table 1: Comparative effects of vincristine sulphate (V) and doxorubicin hydrochloride (D) on haematological parameters in group I and II. Mean values presented here with (±) their respective standard errors

Parameters (Units)	Drug	0 day	7day	14 day	21 day	28 day	Normal values range
Hb (g/dL)	V	12.15^{a} ±0.58	11.03^{b} ±0.74	12.05^{ab} ±0.85	12.35^{ab} ±0.85	13.06^{c} ±0.71	12.00-18.00
	D	12.76^{a} ±0.54	10.96^{b} ±0.42	11.71^{ab} ±0.51	11.75^{ab} ±0.33	12.90^{ab} ±0.46	
TLC ($x10^3/mm^3$)	V	15.27^{a} ±3.24	10.64^{ab} ±1.71	9.72^{b} ±1.37	9.49^{bc} ±1.53	8.24^{c} ±1.06	4.00-15.50
	D	16.43^{a} ±1.74	12.88^{b} ±1.35	12.41^{ab} ±1.43	10.92^{c} ±1.40	9.58^{d} ±1.26	
Neutrophils (%)	V	82.00^{a} ±2.92	79.17^{ab} ±2.46	76.00^{b} ±2.65	75.00^{bcA} ±2.63	72.33^{cA} ±2.15	60.00-75.00
	D	82.00 ±2.19	82.00 ±2.34	81.67 ±1.08	83.16^{B} ±0.65	82.67^{B} ±1.33	
Lymphocytes (%)	V	15.33^{ab} ±3.39	16.50^{a} ±2.60	18.50^{ab} ±2.69	18.33^{ab} ±2.24	19.83^{b} ±1.70	12.00-30.00
	D	15.50 ±2.26	16.00 ±2.17	15.33 ±0.80	14.33 ±0.98	15.16 ±1.42	
Eosinophils (%)	V	0.00 ±0.00	0.33 ±0.33	1.00 ±0.63	1.50 ±0.72	1.00 ±1.00	2.00-10.00
	D	1.16 ±0.83	0.00 ±0.00	1.16 ±0.75	1.66 ±0.80	0.67 ±0.67	
Basophils (%)	V	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.50 ±0.50	0.00-2.00
	D	0.00 ±0.00	0.66 ±0.42	0.66 ±0.42	0.50 ±0.34	0.33 ±0.21	
Monocytes (%)	V	3.00^{aA} ±0.36	4.00^{abA} ±0.85	4.50^{abc} ±1.54	5.16^{bcA} ±1.04	6.33^{cA} ±0.71	3.00-9.00
	D	1.33^{B} ±0.61	1.33^{B} ±0.49	1.16 ±0.47	0.33^{B} ±0.21	1.16^{B} ±0.98	
Thrombocytes ($x10^3/mm^3$)	V	310.50^{a} ±32.16	367.33^{b} ±33.48	395.83^{cA} ±31.55	415.00^{cA} ±28.69	440.00^{dA} ±18.44	170.00-300.00
	D	356.33^{a} ±19.76	300.00^{b} ±26.95	272.00^{bcB} ±22.29	247.83^{bcB} ±12.49	225.16^{cB} ±14.94	
PCV (%)	V	37.67 ±1.67	37.78 ±1.36	37.65 ±1.61	38.18 ±1.46	38.16 ±1.52	36.00-60.00
	D	41.00 ±1.91	37.65 ±1.47	37.31 ±1.44	37.40 ±1.06	37.86 ±0.91	

Values bearing different superscript (a,b,c,d) differ significantly in a row at $p<0.05$

Values bearing different superscript (A, B) differ significantly in a column at $p<0.05$

Table 2: Comparative effects of vincristine sulphate (V) and doxorubicin hydrochloride (D) on biochemical parameters in group I and II. Mean values presented here with (±) their respective standard errors

Parameters (Units)	Drug	0 day	7day	14 day	21 day	28 day	Normal values range
Total Plasma Proteins (g/dL)	V	7.16 ±0.29	7.24 ±0.28	7.26^{A} ±0.25	7.23^{A} ±0.25	7.21^{A} ±0.31	5.00-7.40
	D	6.93^{a} ±0.42	6.38^{ab} ±0.50	6.01^{bB} ±0.42	5.89^{bcB} ±0.47	5.56^{cB} ±0.45	
Albumin (g/dL)	V	3.51^{a} ±0.15	3.46^{ab} ±0.15	3.32^{bA} ±0.13	3.19^{cA} ±0.12	3.02^{dA} ±0.12	2.70-4.40
	D	3.34^{a} ±0.19	2.88^{b} ±0.25	2.74^{bcB} ±0.21	2.55^{cB} ±0.15	2.40^{bcB} ±0.16	
Globulin (g/dL)	V	3.64^{a} ±0.14	3.77^{b} ±0.15	3.94^{Ac} ±0.14	4.03^{d} ±0.14	4.18^{cdA} ±0.21	1.60-3.60
	D	3.58 ±0.26	3.49 ±0.33	3.27^{B} ±0.26	3.33 ±0.36	3.16^{B} ±0.30	
A : G Ratio	V	0.96^{a} ±0.18	0.91^{b} ±0.03	0.83^{c} ±0.02	0.79^{d} ±0.01	0.73^{e} ±0.02	0.80-2.00
	D	0.94^{a} ±0.06	0.85^{ab} ±0.07	0.85^{ab} ±0.06	0.80^{ab} ±0.07	0.77^{b} ±0.04	
AST (IU/L)	V	16.83^{a} ±1.32	19.25^{b} ±1.76	21.18^{c} ±1.94	23.15^{d} ±1.79	26.38^{e} ±1.93	15.00-66.00
	D	22.00^{a} ±2.17	24.38^{ab} ±2.73	28.06^{ab} ±3.21	30.16^{b} ±3.19	35.40^{c} ±3.98	
ALT (IU/L)	V	26.36^{a} ±3.47	29.65^{b} ±3.85	33.61^{ab} ±4.99	37.10^{ab} ±5.18	41.87^{c} ±5.72	12.00-118.00
	D	25.76^{a} ±3.14	30.23^{ab} ±4.88	29.56^{ab} ±6.36	38.03^{b} ±6.03	44.05^{ab} ±8.44	
GGT (IU/L)	V	4.14^{a} ±0.57	4.55^{bA} ±0.57	5.25^{cA} ±0.61	5.78^{dA} ±0.65	6.40^{cdA} ±0.82	1.00-12.00
	D	5.38^{a} ±0.50	6.68^{abB} ±0.71	7.79^{cB} ±0.59	9.84^{dB} ±0.95	11.10^{eB} ±1.34	
Triglycerides (IU/L)	V	72.83^{a} ±7.25	81.83^{ab} ±7.04	91.67^{b} ±7.68	99.83^{c} ±8.87	110.33^{d} ±9.17	29.00-291.00
	D	90.97^{a} ±14.35	98.18^{ab} ±12.95	195.00^{b} ±80.57	102.40^{ab} ±11.52	110.18^{ab} ±15.25	
ALP (IU/L)	V	76.85^{a} ±5.70	93.48^{b} ±6.34	104.56^{c} ±6.89	118.85^{d} ±12.15	130.85^{e} ±13.42	5.00-131.00
	D	73.26^{a} ±3.49	88.56^{b} ±5.96	100.76^{c} ±7.07	115.58^{d} ±8.31	135.67^{e} ±10.45	
Cholesterol (mg/dL)	V	173.17^{a} ±7.37	184.33^{ab} ±8.41	193.50^{ab} ±8.32	203.00^{ab} ±12.27	215.67^{b} ±10.80	92.00-324.00
	D	213.55^{a} ±17.44	233.13^{b} ±16.42	270.13^{c} ±12.89	295.45^{d} ±7.07	324.67^{e} ±5.27	
Direct Bilirubin (mg/dL)	V	0.10^{a} ±0.03	0.14^{b} ±0.04	0.20^{c} ±0.05	0.24^{abA} ±0.06	0.28^{bcA} ±0.05	0.00-0.20
	D	0.06 ±0.01	0.06 ±0.01	0.08 ±0.02	0.05^{B} ±0.01	0.08^{B} ±0.01	
LDH (IU/L)	V	185.17^{a} ±23.40	214.33^{bA} ±17.64	242.67^{cA} ±17.67	276.00^{d} ±25.72	294.83^{eA} ±28.64	140.00-280.00
	D	231.16^{a} ±12.64	271.67^{bB} ±12.09	302.83^{cB} ±17.24	328.00^{d} ±15.43	368.17^{eB} ±12.95	
CK (IU/L)	V	107.78^{a} ±20.63	177.30^{b} ±28.70	222.30^{c} ±26.97	268.30^{d} ±39.83	303.90^{e} ±43.03	59.00-895.00
	D	73.85^{a} ±12.56	124.63^{b} ±8.66	181.90^{c} ±12.85	240.63^{d} ±21.83	278.56^{e} ±25.75	
BUN (mg/dL)	V	10.73 ±0.48	10.79 ±0.49	10.79 ±0.58	10.85 ±0.54	10.89 ±0.48	6.00-25.00
	D	9.22^{a} ±0.98	10.02^{b} ±1.12	10.61^{c} ±1.07	11.13^{bc} ±0.93	11.85^{d} ±0.84	
Creatinine (mg/dL)	V	1.08^{a} ±0.08	1.21^{ab} ±0.06	1.24^{ab} ±0.08	1.33^{b} ±0.08	1.27^{ab} ±0.06	0.50-1.60
	D	0.83 ±0.13	0.95 ±0.12	0.89 ±0.09	1.02 ±0.15	1.01 ±0.10	
Cortisol (µg/dL)	V	1.33^{a} ±0.03	1.39^{ab} ±0.03	1.42^{ab} ±0.06	1.40^{ab} ±0.01	1.46^{b} ±0.03	0.60-1.90
	D	1.34 ±0.04	1.40 ±0.03	1.37 ±0.03	1.40 ±0.05	1.44 ±0.05	
Glucose (mg/dL)	V	118.03^{aA} ±6.28	129.48^{ab} ±10.87	137.51^{bA} ±8.77	139.73^{ab} ±13.08	134.85^{ab} ±9.88	70.00-138.00

	D	98.78^{B} ±3.49	105.86 ±7.19	106.53^{B} ±7.79	108.93 ±7.89	107.67 ±6.15	
Calcium (mmol/L)	V	8.03 ±0.56	8.01 ±0.46	7.91 ±0.40	7.97 ±0.44	8.18 ±0.53	8.90-11.40
	D	7.28 ±0.42	7.24 ±0.54	7.33 ±0.46	7.70 ±0.39	7.54 ±0.52	
Chloride (mmol/L)	V	85.02 ±3.73	85.50 ±4.13	85.98 ±3.67	85.25 ±3.60	86.16 ±3.70	102.00-120.00
	D	82.15 ±1.60	81.33 ±1.53	81.90 ±1.32	82.46 ±1.51	82.68 ±1.61	
Magnesium (mmol/L)	V	1.48 ±0.11	1.54 ±0.11	1.55^{A} ±0.10	1.58 ±0.08	1.56^{A} ±0.11	1.20-1.90
	D	1.54^{a} ±0.12	1.75^{b} ±0.13	2.01^{cB} ±0.17	1.88^{bc} ±0.35	2.41^{dB} ±0.11	
Phosphorus (mmol/L)	V	3.75 ±0.29	3.78 ±0.24	3.76 ±0.25	3.86 ±0.32	3.89 ±0.32	2.50-6.00
	D	3.49 ±0.28	3.61 ±0.49	3.48 ±0.44	3.76 ±0.46	3.69 ±0.60	
Potassium (mmol/L)	V	4.19 ±0.11	4.25 ±0.13	4.31 ±0.08	4.35 ±0.12	4.34 ±0.11	3.60-5.50
	D	4.38 ±0.19	4.44 ±0.18	4.46 ±0.14	4.55 ±0.15	4.39 ±0.17	
Sodium (mmol/L)	V	145.53 ±1.95	145.87 ±1.87	146.33 ±1.85	146.75 ±1.90	146.15 ±1.84	139.00-154.00
	D	145.05 ±1.56	145.56 ±1.07	145.93 ±0.90	130.00 ±16.42	145.13 ±1.59	

Values bearing different superscript (a, b, c, d) differ significantly in a row at $p<0.05$
Values bearing different superscript (A, B) differ significantly in a column at $p<0.05$

No significant change in total plasma proteins was observed in group I while significant decrease was observed in group II. The decrease in total proteins in group II could be due to hepatotoxicity or inappetence [10]. There was a significant decrease in albumin and A:G ratio and significant increase in globulin in group I while in group II, there was a significant decrease in albumin and A:G ratio while no significant change was observed in globulin levels. The decreased albumin could be due to inappetence [10], hepatotoxicity or nephrotoxicity [11]. The increased globulin could be due to hepatotoxicity, acute inflammatory processes or any infection [12]. The decrease in A:G ratio could be due to combined effects of both i.e. decrease in albumin and increase in globulin or change in any one of these.

There was a significant increase in AST, ALT, GGT, triglycerides, ALP, cholesterol and direct bilirubin in group I. Similar results were obtained in group II during study except that no significant change was observed in direct bilirubin. Their increased value could be due to the drug induced hepatotoxicity. Similar results were obtained in cases of CTVT treated with vincristine sulphate [13]. Behara *et al.* [14] also observed same results after doxorubicin therapy.

There was a significant increase in LDH and CK values in both the groups (I and II). Measurement of LDH is not organ specific but increased LDH indicates myonecrosis and variety of hepatic disorders [15]. The increased CK value can be used to detect acute toxicity in cardiac and skeletal muscles [16]. Sindhur [17] also obtained similar results during his study.

There was no significant change in BUN while a small but significant increase in creatinine value at 21st day was observed in group I. In group II, significant increase in BUN was observed upto 28th day but no significant change in creatinine was observed. Similar results were obtained by Todorova *et al.* [2] in dogs undergoing chemotherapy for mammary tumour.

Cortisol increased significantly and glucose increased non-significantly in group I while no significant change was observed in group II. The increase in cortisol was marginal and could be due to the stress due to handling. The increase in glucose could be due to dietary intake but was non-significant. No significant changes in the electrolytes were observed in both the groups except for a significant increase in magnesium in group II. The increase in magnesium could be due to the cytotoxic effect of doxorubicin which cause cell lysis and release of intracellular magnesium into blood [18]. On the basis of this study, both the chemotherapeutic drugs are found to cause bone marrow suppression, hepatotoxicity and nephrotoxicity.

4. References

1. Dhami MA, Tank PH, Karle AS, Vedpathak HS, Bhatia AS. Epidemiology of canine mammary gland tumours in Gujarat. Vet. World. 2010;3(6):282-285.
2. Todorova I, Simeonova G, Simeonov R, Dinev D. Efficacy and Toxicity of Doxorubicin and Cyclophosphamide Chemotherapy in dogs with spontaneous mammary tumours. Trakia J Sci. 2005;3(5):51-58.
3. Dobson JM, Hohenhaus AE, Peaston AE. Cancer chemotherapy. In: Small Animal Clinical Pharmacology 2nd ed. Saunders Elsevier, Edinburgh, 2008, 330-336.
4. Said RA, Silva LF, Albuquerque AROL, Sousa-Neta EM, Lavinsky MO. Efficacy and side effects of vincristine sulphate treatment on canine transmissible venereal tumour. 2009; In: Proceedings of 34th World Small Animal Veterinary Congress - São Paulo, Brazil.
5. Sandhu HS, Ramphal S. Essentials of Veterinary Pharmacology and Therapeutics, 1st ed, 2006, 1359-1381.
6. Dobson JM, Gorman, NT. Cancer chemotherapy. In: Small Animal Practice. Blackwell scientific publication, London, 1993, 67-154.
7. Yadav A, Bugalia NS, Pandey AK. Haemato-biochemical and therapeutic evaluation of doxorubicin and vincristine in canine transmissible venereal tumour. Indian J Anim.

Reprod. 2017;39(2):40-42.
8. Ahn YS, Byrnes JJ, Harrington WJ, Cayer ML, Smith DS, Brunskill DE, *et al*. The treatment of idiopathic thrombocytopenia with vinblastine-loaded platelets. *N*. Engl. J Med. 1978;298:1101-1107.
9. Klaassen JK. Reference Values in Veterinary Medicine. Lab. Med. 1999;30(3):194-197.
10. Umeki S. Biochemical abnormalities of the serum in anorexia nervosa. J Nerv. Ment. Dis. 1988;176(8):503-506.
11. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: Pathogenesis and Clinical Significance. J. Parenter. Enter. Nutr, 2018, 1-13.
12. Feinstein AR, Petersdorf RG. The clinical significance of hyperglobulinemia. I. Diagnostic implications. Ann. Intern. Med. 1956;44(5):899-924.
13. Daleck CL, Daleck CM, Ferreira H, Santana AE. New studies on treatment of canine transmissible venereal tumor (TVT). Ars. Veterinaria. 1987;3:203-209.
14. Behera SK, Kurade NP, Monsang SW, Das DP, Sharma KK, Mohanta RK. Clinico pathological findings in a case of canine cutaneous metastatic transmissible tumour. Vet. Arhiv. 2012;82(4):401-410.
15. Velberg SJ. Skeletal muscle function. In: Clinical biochemistry of domestic animals, 6th ed. Academic Press, 2008, 472-744.
16. Cardinet GH. Skeletal muscle function. In: Clinical Biochemistry of Domestic Animals. Academic Press, San Diego, CA, 1997, pp: 407-440.
17. Sindhur A. Endoscopic assessment of buccal, oesophageal and gastric mucosa following doxorubicin hydrochloride administration in dogs; M.V.Sc. thesis submitted to Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar, 2017.
18. Sartori S, Nielsen I, Tassinari D, Maestri A, Abbasciano V. Intracellular magnesium concentrations and acute anthracycline-induced cardiotoxicity. Br. J Cancer. 1991;64:785-787.