The Pharma Innovation Journal 2021; SP-10(1): 159-161

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2021; SP-10(1): 159-161

www.thepharmajournal.com
Received: 16-11-2020
Accepted: 18-12-2020

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Haematological and serum biochemical changes associated with surgical oncology of canine mammary and superficial neoplasms in dogs

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Abstract
Hematological and biochemical parameters were studied during the surgical management of clinical cases of mammary and superficial neoplasms in thirty six dogs. The dogs were studied in three groups of twelve animals each as group- I with surgery alone, group –II with neoadjuvant chemotherapy followed by surgery and group – III with surgery followed by adjuvant chemotherapy. Vinblastine- Prednisolone and Doxorubicin - Prednisolone chemotherapy protocols was adopted in six animals each in group II and III. The haematological and biochemical parameters were interpreted using repeated measures ANOVA to test the variance within the three groups on biweekly interval observations and to test the significance between three groups. Statistically significant variation ($P<0.05$) on mean haemoglobin, mean platelet count, Total leucocyte count, Differential Leucocyte Count (DLC) and biochemical parameters -ALP ,BUN and Creatinine values were observed within the groups and between the groups with marked change on the day of presentation in animals of group III with advanced stages of neoplasm. Hematological and biochemical parameters also showed as significant variations after the chemotherapy.

Keywords: haematological, biochemical, neoadjuvant,, adjuvant chemotherapy, mammary neoplasm, superficial neoplasms, dogs

1. Introduction
Cancer-related hematologic disorders results in a decrease or increase in the absolute circulating blood components that potentiates alterations in hemostasis manifested as cancer-induced neutrophilic leukocytosis, lymphocytosis and blood dyscrasias along with chronic inflammatory changes, tissue necrosis and stress. Canine mammary and skin./subcutaneous neoplasms results in a reduction in mean haemoglobin, PCV and TEC when compared to that of apparently healthy animals. (Todorova *et al*., 2005) [11]. Anaemia could be regarded as the most common hematologic abnormality encountered in cancer patients which accounts for 30 to 50 per cent of patients with solid tumours and 40 to 70 per cent in hematopoietic tumours. (Miller *et al.*, 2009) [7]. Early detection of variations in biochemical parameters in canine mammary and skin/ subcutaneous neoplasms helps in formulating the treatment strategies and aids in predicting the prognosis of cancer treatment. (Chopra and Saxena.1997) [2]. The present study was conducted to study the hematological and biochemical changes associated with the surgical management of canine mammary and skin/ subcutaneous neoplasms in dogs.

2. Materials and Methods
Thirty six clinical cases of canine mammary and skin/ subcutaneous neoplasms in dogs presented to the University Veterinary Hospitals of Kerala Veterinary and Animal Sciences University were subjected to surgical management in three groups consisting of twelve animals each. In group –I, animals with neoplasms having well-defined surgical margins were subjected to surgery alone on day 0 and three biweekly hematological and biochemical observations were done postoperatively on days 14, 28 and 42 respectively. In group II, animals with neoplasms having inflammatory changes with poor / ill-defined surgical margins were subjected to two cycles of neoadjuvant chemotherapy on day 0 and day 14 followed by surgery on day 28 and three biweekly observations were made on 41, 56 and 70 days respectively. In group III, malignant neoplasms with pulmonary metastases were managed by surgery on day 0 followed by two adjuvant chemotherapy cycles on day 14 and day 28 and three biweekly observations were taken on days 42, 56 and 70 days respectively.

The chemotherapy was carried out using the using VP protocol using vinblastine @ 2 mg/ m^2 intravenously and prednisolone @ 1 mg/kg bwt intramuscularly or DP protocol using DP protocol using doxorubicin @ 18 mg/ m^2 and prednisolone @ 1 mg/kg bwt) at the biweekly intervals. Two ml whole blood was collected in EDTA for evaluation of haematological parameters including haemoglobin concentration (Hb), the volume of packed red cells (VPRC), total leukocyte count (TLC), total erythrocyte count (TEC) , differential leukocyte count (DLC) and platelet count using automatic haematology analyzer. The serum was separated from the blood collected without anticoagulant by centrifuging at 3000 rpm for five minutes. Blood urea nitrogen (mg/dL) (estimated by diacetyl monoxime method), Serum creatinine concentration (mg/dL) (estimated using Jaffe's alkaline picrate method) and levels of Alkaline phosphatase (ALP) IU/L were estimated using standard kits in semi-automated biochemical analyser on the day of presentation followed by biweekly intervals. The results were statistically analyzed using SPSS version 24 using repeated measures ANOVA to test the variance within the three groups on biweekly interval observations , The level of significance was fixed at 5% ($P<0.05$).

3. Results and Discussion

3.1 Hematological parameters

The hematological parameters in each group of animals are described in table -1.

In group I, a statistically significant increase in platelet count and Total erythrocyte count ($P<0.05$) was observed on 42nd day. Differential Leucocyte Count revealed statistically significant agranulocytosis and lymphocytosis on day 42 compared to day 0 and day 21 and statistically significant low monocyte value on day 42. This improvement of parameters could be attributed to the improvement in condition of the animal after the surgery as documented by Finora (2003) [4].

In dogs of group II, mean haemoglobin values, mean platelet count , erythrocyte count and differential leucocyte count showed statistically significant reduction on days 14 and 28 and increase on day 42 followed by statistically significant increase on day 56 and day 70. Significant increase in platelet count was observed on animals which received vinblastine prednisolone neoadjuvant chemotherapy protocol. This findings were in agreement with Fresneau *et al*. (2011) [5]. Differential leukocyte counts showed statistically significant low values after neoadjuvant chemotherapy in this group. This could be attributed to the cytotoxic and myelosuppressive effects of chemotherapy as stated by Spivak *et al*. (2009) [9]. All the animals in group II showed improved blood values after three weeks of surgery and these findings justified the clinical improvement of the patients.

In group- III animals, mean CBC values were low with a prominent granulocytosis and anaemia. This could be attributed to the advanced metastatic neoplasms in this group. Schultz (2010) [10] and Childress (2012) [1] had reported similar observations in oncologic patients. The significant findings of neutropenia on 28th and 42nd day could be attributed to the adverse effect of adjuvant chemotherapy as reported by Spivak *et al*. 2009 [9]. The regaining of normal values by 70th-day observation substantiated clinical improvement of animals in this group. Statistically significant lower haemoglobin values and VPRC values in group III on day 0 could be attributed to the clinical severity of the cases as this group contained malignant metastatic neoplasms. Significant reduction in the leukocyte values in group III on day 28 could be attributed to the effect of adjuvant chemotherapy. Similar findings were documented by Mitra *et al*. (2001) [8] and Klopfleisch (2016) [6].

3.2 Serum biochemical parameters

Mean serum biochemical values of animals within and between the are described in table 2.

Animals of group I showed no significant variation in values between days of observations with regard to mean ALP, mean BUN values and mean creatinine values**.** In group II, mean ALP values and mean BUN values showed a statistically significant decrease ($P<0.05$) on day 14 as 64.42 ± 9.32 IU/L and a significant increase on day 42 with significance difference between 0 and 14th day of observations within the group. The group III animals showed elevated values of mean ALP, mean BUN values, mean creatinine on days 0 and 14 and 28, 42, 56 and 70 with no significant difference between days of observations within the groups. These changes could be due to the malignancy and findings were in agreement with Chopra and Saxena (1997) [2] who reported a significant increase in alkaline phosphatase in mammary neoplasm. Even though there were variations in the BUN and Creatinine values in the animals between groups on days 0, 14 and days 70 among the groups, variations were within the normal range.

Table 1: Mean haematological values of the animals within the group

	Parameter	DAYS					
		0 Mean ± SE	**14 Mean ± SE**	**28 Mean ± SE**	**42 Mean ± SE**	**56 Mean ± SE**	**70 Mean ± SE**
Group-I	Hb (g/dL)	11.53 ± .39^{a}	11.87 ± .29^{a}	12.11 ± .19 ^{a}	11.79 ± .27^{a}		
	PC x 10^3/µL	237.25 ± 23.31 ^{a}	256.50 ± 26.92 ^{ab}	267.83 ± 20.11 ^{b}	292.50 ± 15.26^{c}		
	TEC x 10^3 /µL	4.84 ± 0.22 ^{a}	5.03 ± 0 .37 ^{a}	5.04 ± 0.18 ^{a}	5.05 ± 0 .13 ^{a}		
	TLC x 10^3 /µL	16.95 ± .630 ^{a}	19.18 ± .83 ^{b}	19.02± .58 ^{b}	21.72 ± 1.25 ^{c}		
	Granulocyte (%)	73.04 ± .93 ^{bc}	74.03 ±.48 ^{c}	71.38 ± .46 ^{b}	69.80 ± .45^{a}		
	Lymphocyte (%)	20.28 ± .75 ^{a}	20.73 ± .48 ^{a}	22.59 ± .39 ^{b}	23.26 ± .42 ^{c}		
	Monocyte (%)	6.68 ± .58 ^{bc}	5.24 ± .24 ^{a}	6.03 ± .24 ^{b}	6.94 ± .18 ^{c}		
	VBL-PRC (%)	33.75 ± .87 ^{a}	34.83 ± 1.10 ^{ab}	36.42 ± .73 ^{b}	37.17 ± .91 ^{b}		
Group-II	Hb (g/dL)	10.07 ± .35 ^{a}	9.56 ± .30 ^{b}	8.87 ± . 42 ^{b}	9.13± .48 ^{b}	11.03 ± .340 ^{c}	11.99 ± .25 ^{d}
	PC x 10^3/µL	182.83 ± 18.28^{ad}	242.43 ± 35.43^{ac}	320.83 ± 61.39 ^{bd}	273.25 ± 19.68 ^{bc}	234.92 ± 9.75 ^{bc}	212.75 ± 6.93 ^{ad}
	TEC x 10^3 /µL	3.65 ± 0.35 ^{a}	4.55 ± 0.32 ^{bc}	4.86 ± 0.22 ^{bc}	4.47 ± 0.09 ^{ab}	5.26 ± 0.15^{c}	4.70 ± 0.15^{b}
	TLC x 10^3 /µL	20.17 ± .37 ^{d}	19.12 ± .29 ^{bc}	18.05 ± .26^{a}	18.64 ± .31 ^{ab}	19.66 ± .36^{cd}	19.84 ± .30^{d}
	Granulocyte (%)	72.70 ± 1.42 ^{bc}	72.63 ± .79 ^{b}	75.23 ± .64 ^{c}	74.29 ± .90 ^{bc}	72.82 ± 1.03 ^{bc}	68.88 ± .47 ^{a}
	Lymphocyte (%)	20.35 ± 1.1^{cd}	18.23 ± .88 ^{b}	15.33 ± .74 ^{a}	18.67 ± .77 ^{bc}	20.68 ± .85^{d}	24.18 ± .50 ^{e}
	Monocyte (%)	6.95 ± .40 ^{a}	9.15 ± .27 ^{b}	9.45 ± .25 ^{b}	7.04 ± .46 ^{a}	6.50 ± .36 ^{a}	6.94 ± .19 ^{a}
	VBL-PRC (%)	34.42 ± 1.59 ^{a}	37.00 ± 1.50 ^{ab}	37.08 ± 1.07 ^{ab}	35.42 ± 1.03 ^{a}	40.25 ± 1.14 ^{bc}	41.50 ± 1.17 ^{c}

Group-II	Hb (g/dL)	8.500 ± .53 ab	9.83 ± .52 cd	7.99 ± .43 ab	7.87 ± .27 a	9.01 ± .49 bc	11.08 ± .46 d
	PC x 10^3/µL	102.75 ± 4.51 a	155.50 ± 17.04 b	169.08 ± 20.68 b	226.08 ± 30.57c	214.75± 23.22 d	223.42 ±18.35 cd
	TEC x 10^3 /µL	3.27 ± .16 ab	4.14 ± .25 cd	2.86 ± .23 a	3.65 ± .13bc	3.54 ± .22 bc	4.25 ± .14 d
	TLC x 10^3 /µL	19.99 ± .95 c	18.54 ± 1.37 bc	13.50 ± .70 a	12.36 ± .40 a	16.73 ± .81 b	19.58 ± .30 c
	Granulocyte (%)	73.67 ± 0.94 b	77.35 ± 0.85 c	78.33 ± 1.18 c	75.21 ± 1.03 bc	74.43 ± 0.86 b	69.30 ± 0.48 a
	Lymphocyte (%)	19.18 ± 0.80 b	17.14 ± 0.88 ab	16.58 ± 0.92 a	17.90 ± 0.67 a	17.32 ± 0.61 a	23.76 ± 0.49 c
	Monocyte (%)	7.16 ± 0.50 bc	5.51 ± 0.39 a	5.09 ± 0.30 a	6.89 ± 0.45 bc	8.25 ± 0.61c	6.94 ± 0.19 b
	VBL-PRC (%)	29.33 ± .75a	33.25 ± .99 b	30.00 ± 1.40 a	29.42 ± .87 a	30.42 ± 1.72 ab	37.75 ± 2.02 c

Figures bearing different superscripts in each row differ significantly ($p \leq 0.05$)

Table 3: Mean serum biochemistry values of animals within the group (Mean±S.E)

	Parameter	DAYS					
		0 Mean ± SE	14 Mean ± SE	28 Mean ± SE	42 Mean ± SE	56 Mean ± SE	70 Mean ± SE
Group-I	ALP(IU/L)	85.75 ± 10.18 a	107.75 ± 14.100 a	89.58 ± 10.767 a	93.42 ± 8.03 a		
	BUN (mg/dl)	22.83 ± 1.16 a	29.50 ± 2.70 a	25.50 ± 1.88 a	24.33 ± 1.96 a		
	Creatinine (mg/dl)	1.243 ± .118 b	1.307 ± .079 b	1.137 ± .066 ab	0.964 ± .042 a		
Group-II	ALP(IU/L)	111.17 ± 9.55 bc	64.42 ± 9.32 a	120.75 ± 7.02 bcd	157.00 ± 19.72 cd	143.83 ± 11.11 d	110.17 ± 6.59 b
	BUN (mg/dl)	26.00 ± 1.53 ab	22.25 ± 1.61 a	24.92 ± 1.77 abc	31.33 ± 2.37 c	30.42 ± 2.75 abc	28.67 ± 2.05 bc
	Creatinine (mg/dl)	1.19 ± 0.12 a	1.63 ± 0.15 b	1.23 ± 0.12 ab	1.32 ± 0.07 ab	1.31 ± 0.14 ab	1.24 ± 0.13 ab
Group-III	ALP(IU/L)	134.67 ± 9.83 a	149.58 ± 9.10 a	155.17 ± 12.45 a	141.42 ± 7.24 a	131.50 ± 10.44 a	122.08 ± 8.37 a
	BUN (mg/dl)	35.75 ± 2.14 ab	34.75 ± 1.49 ab	37.25 ± 1.55 b	37.83 ± 1.10 b	33.92 ± 1.85 ab	30.17 ± 2.04 a
	Creatinine (mg/dl)	1.48 ± 0.11c	1.31 ± 0.14abc	1.39 ± 0.09bc	1.41 ± 0.10c	1.16 ± 0.09ab	1.05 ± 0.06a

Figures bearing different superscripts in each row differ significantly ($p \leq 0.05$)

Conclusion

It can be concluded that the variations in the hematological and biochemical parameters on the day of presentation in animals could be directly related to the clinical stages and malignancy of neoplasms. The chemotherapy increased the prevalence of anemia with thrombocytopenia as in doxorubicin-prednisolone chemotherapy and a thrombocyte enhancing effect with vinblastine prednisolone chemotherapy. The relatively higher values returned to normal values on day 70 can be concluded as symptomatic improvement due to therapy.

Ethical approval

The study was conducted on clinical cases of neoplasms presented to the university veterinary hospitals hence ethical approval was not needed. All the samples were collected as a part of routine diagnostic and treatment protocol after taking written consent from the owners.

Acknowledgements

The authors acknowledge Kerala Veterinary and Animal Sciences University (KVASU) for facilities provided for the research work.

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