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Clinico, haemato-biochemical changes and therapeutic management of canine ehrlichiosis

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Abstract

Canine ehrlichiosis is a multisystemic, infectious disease caused by a number of pleomorphic rickettsial organisms belonging to *Ehrlichia* species. Ehrlichia an obligate intracellular organism that resides as a micro colony within a membrane-lined intracellular vacuole (morulae), primarily within monocytes and macrophages of dogs. Ehrlichiosis is characterized by acute, sub-acute and chronic form with varied clinical signs. diagnosis of canine ehrlichiosis is based on clinical signs, haemato-biochemical changes, identification of morulae in blood smear and buffy coat smear, serological and molecular techniques. Since there are few studies investigating the clinico, haemato-biochemical changes and therapeutic management of canine ehrlichiosis in India. Further, study of Canine Monocytic Ehrlichiosis has not been explored in Bidar (Karnataka state) till date, therefore, keeping in view the above issues the present study was undertaken to know the clinico, hemato-biochemical changes and therapeutic management of canine ehrlichiosis. In the present study, lymphadenopathy was the most predominant clinical sign followed by pyrexia, depression, bleeding tendencies (epistaxis), icteric mucous membrane, ascites and lameness. Anaemia, thrombocytopenia, monocytopenia, elevation of BUN, creatinine, ALT along with hypoproteinemia, hypoalbuminemia and hyperglobulinemia were the major haemato-biochemical changes in ehrlichiosis affected dogs. Imidocarb dipropionate was found to be more efficacious in treating canine ehrlichiosis compared to combination of oxytetracycline and doxycycline along with papaya leaf extract (caripill®) in terms of faster recovery and mean treatment days. Hence, imidocarb dipropionate can be used for successful therapeutic management of canine ehrlichiosis.

Keywords: Ehrlichiosis, lymphadenopathy, anaemia, thrombocytopenia, imidocarb dipropionate, caripill

Introduction

Canine ehrlichiosis is a multisystemic, infectious disease caused by a number of pleomorphic rickettsial organisms belonging to *Ehrlichia* species. Ehrlichia an obligate intracellular organism that resides as a micro colony within a membrane-lined intracellular vacuole (morulae), primarily within monocytes and macrophages of dogs (Simpson, 1972) [34]. *E. canis* is acknowledged as the primary causative agent of Canine Monocytic Ehrlichiosis (CME) (Bulla *et al.*, 2004) [5]. The disease was initially described by Donatein and Lestoquard in 1935 in Algeria. It has also been previously acknowledged as canine rickettsiosis, canine haemorrhagic fever, tracker dog disease, canine tick typhus, nairobi bleeding disorder and tropical canine pancytopenia. The disease is mainly transmitted by the bite of brown dog-tick *Rhipicephalus sanguineus* and occurs as acute, sub-clinical and chronic form. The clinical signs usually described in Canine ehrlichiosis includes fever, depression, anorexia, weight loss, haemorrhages, epistaxis, gastrointestinal disturbances like vomiting or diarrhoea, respiratory disorders and ocular signs; laboratory findings most frequently observed are thrombocytopenia, leucopenia, anaemia and hyper-gammaglobulinaemia (Woody and Hoskins, 1991) [40]. The diagnosis of canine ehrlichiosis is based on characteristic hematological and biochemical abnormalities along with microscopic evaluations of stained blood smears and buffy coat smears, serological and molecular techniques. Since there are few studies investigating the clinico, haemato-biochemical changes and therapeutic management of canine ehrlichiosis in India. Further, study of Canine Monocytic Ehrlichiosis has not been explored in Bidar (Karnataka state) till date, therefore, keeping in view the above issues the present study was undertaken to know the clinico, hemato-biochemical changes and therapeutic management of canine ehrlichiosis.

Materials and methods

A total of 33 dogs aged 4-7 years presented to Out Patient Ward (Medicine), Veterinary College, Bidar and Veterinary Hospital, Disease Diagnostics and Information Centre, APMC (Agriculture Product Marketing Committee) yard, Bidar with a history of anorexia, pyrexia, inappetance, epistaxis and tick infestation suggestive of canine ehrlichiosis were included for clinico, haemato-biochemical study.

Haemato-biochemical study

For haemato-biochemical study, around 5ml of blood was collected in sterile vials under aseptic conditions from ehrlichiosis affected dogs. 1 ml blood sample from each animal was utilised for haematological estimation and blood smear preparation. Remaining blood sample was processed for serum collection.

Haematological parameters (haemoglobin, packed cell volume, total erythrocyte count, total leucocyte count, differential leucocyte count and platelet count) were estimated with the help of fully automated haematology cell counter-Automatic Blood Cell Counter, Model PCE 210, Manufactured by ERMA Inc., Tokyo, Japan.

Serum samples were utilized for the estimation of biochemical parameters like blood urea nitrogen, creatinine, total protein, albumin, globulin and albumin:globulin ratio by ARTOS[®] semi automatic biochemical analyser using kits. The diagnosis of canine ehrlichiosis was confirmed either by detection of morulae of *E.canis* in Wright-Giemsa stained blood smear or buffy coat smear or by ELISA based SNAP 4Dx kit.

Therapeutic study

A total of sixteen ehrlichiosis positive dogs (16) were randomly divided into Group I and Group II, each group consisting of eight animals. Group I dogs were treated with inj oxytetracycline @ 22 mg/kg IV diluted with normal saline for 2 days followed by tab doxycycline @ 10 mg/kg orally for 19 days and tab *Carica papaya* leaf extract (caripill[®]) orally once daily for 7 days whereas, Group II dogs were treated with single dose of inj imizol[®] (Imidocarb dipropionate, manufactured by INTERVET) @ 5 mg/kg deep IM. Ancillary treatment for both the groups included syrup dexorange[®] @ 5 ml bid orally 10 days, inj prednisolone @ 1 mg/kg BW IM in tapering doses and inj melonex for 3-5 days IM.

Statistical analysis

The haemato-biochemical values obtained in the affected groups and control group were subjected to statistical analysis by one way ANOVA using Statistical Package for Social Sciences (SPSS) Version 20. Significance was set at 5 per cent ($p \leq 0.05$) level.

Results and discussion

The clinical findings in ehrlichiosis infected dogs are depicted in Fig. 1. Of the 33 ehrlichiosis infected dogs, lymphadenopathy (87.88%) was the most predominant sign followed by pyrexia (84.88%), depression (78.78%), anorexia (72.73%), tick infestation (69.69%), pale conjunctival mucous membrane (51.52%), congested (39.39%) and bleeding tendencies (30.30%). Icteric mucous membrane (09.09%), vomiting and ascites (06.06%) and lameness (03.03%) were other signs recorded. Similar findings were reported by Kumar *et al.* (2010)^[22]; Dhankar *et al.* (2011)^[7] and Dixit *et al.* (2012)^[9]. Replication of the organisms in the reticulo-

endothelial system along with proliferation of medullary and paracortical lymphocytes and aggregation of reactive histiocytes in the lymph nodes resulted in generalized lymphadenopathy (Harrus *et al.*, 1997 and Singla *et al.*, 2011)^[16, 35]. Loss of blood due to thrombocytopenia, suppression of bone marrow and probably due to immune mediated red cell destruction resulted in pallor mucosae (Buhles *et al.*, 1974)^[4]. Dhankar *et al.* (2011)^[7] opined that bleeding tendencies (epistaxis, malena, haematemesis, petechial and ecchymotic haemorrhages on oral gums and ventral abdomen) was mainly due to thrombocytopenia and damage to vascular endothelium due to deposition of immune complexes on the vascular wall. Hypoalbuminaemia and vasculitis has been attributed as the reason of oedematous tendencies i.e. ascites in canine ehrlichiosis (Randhawa *et al.*, 2011 and Simpson, 1972)^[32, 34]. Lameness (03.03%) in ehrlichiosis affected dogs might be attributed to polyarthritis. Similar findings were reported by Thilagar *et al.* (1990)^[37] and Buoro *et al.* (1990)^[6].

The haemato-biochemical parameters were evaluated in ehrlichiosis affected dogs. A comparative analysis of haematological parameters are tabulated in Table (1). The haemogram (Haemoglobin, total erythrocyte count and PCV) in affected animals (8.12 ± 0.96 , 3.58 ± 0.46 and 25.09 ± 3.01) were significantly reduced ($p \leq 0.05$) when compared with healthy control group (14.69 ± 0.19 , 7.12 ± 0.09 and 44.55 ± 0.89) indicative of severe anaemia. The results of the present study were in close confirmation with the reports of Oliveira *et al.* (2000)^[29], Tsachev *et al.* (2013)^[38] and Kottadamane *et al.* (2016)^[20]. Low haemogram in canine ehrlichiosis is mainly because of loss of blood due to thrombocytopenia, suppression of bone marrow and probably immune mediated destruction of red blood cells (Buhles *et al.*, 1974)^[4]. Lilliehork *et al.* (1998)^[24] cited that release of proinflammatory cytokine in response to canine ehrlichiosis inhibit the secretion of erythropoietin and colony forming erythroid resulting in decreased RBC production. There was a significant decrease in total platelet count in the affected dogs (83.50 ± 11.35) compared to healthy animal (400.75 ± 13.62) indicative of severe thrombocytopenia. Thrombocytopenia as hallmark of canine ehrlichiosis has been reported by Greene *et al.* (1985)^[15]; Kuehn and Gaunt (1985)^[19] Macieira *et al.* (2005)^[25] and Kottadamane *et al.* (2016)^[20]. Marked thrombocytopenia noted during the present study might be attributed to decrease in circulating half life of platelets, dysfunction of platelets and / or production of anti-platelet antibodies and increase in platelet destruction. However, immune mediated thrombocytopenia by the immune mediated destruction, sequestration or by decreased production, vasculitis and platelet function abnormalities has also been reported by Lappin (2009)^[23]. There was a non significant difference in total leucocyte count, neutrophils, eosinophils, basophils and lymphocytes when compared to control group. Whereas, there was a significant decrease ($P \leq 0.05$) in the monocyte values on the day of presentation which is in agreement with Podhade *et al.* (2009)^[30] and Tsachev *et al.* (2013)^[38]. Ettinger and Feldman (2000)^[10] postulated that some monocytes infected with *Ehrlichia canis* would adhere to the vascular endothelium, leading to reduction in their peripheral blood numeration. A comparative analysis of biochemical parameters are tabulated in Table (2). The mean values of serum BUN and creatinine were significantly elevated ($p \leq 0.05$) in affected dogs compared to the healthy control group suggestive of

uraemia, similar findings were reported by Niwetpathomwat *et al.* (2006) [28] and Adrian *et al.* (2016) [1]. An increase in BUN in canine ehrlichiosis might be due to immune complex mediated glomerulonephritis (Harrus *et al.*, 1998) [17]. There was a significant increase in ALT values in affected dogs when compared to the control group which could be attributed to the underlying hepatic injury as reported by Reardon and Pierce (1981) [33]. There was a significant decrease ($P \leq 0.05$) in total proteins in canine ehrlichiosis affected dogs compared to healthy control group indicating hypoproteinemia which is in accordance with the earlier reports of Barbara *et al.* (1996) [2] and Bhadesiya and Raval (2015) [3]. However, Harrus *et al.* (1997) [16] and Smitha and Vijaykumar (2014) [36], reported hyperproteinemia in dogs affected with ehrlichiosis. Hypoproteinemia seen in the present study could be attributed to compromised hepatic function. Elevated globulins and resultant decrease in albumin observed in present investigation had reflected in the form of significant decrease ($P \leq 0.05$) in A:G ratio which corroborates with the earlier reports of Greene *et al.* (1985) [15]; Barbara *et al.* (1996) [2]; Smitha and Vijaykumar (2014) [36] and Kottadamane *et al.* (2016) [20]. Persistence of higher values of globulin might be attributed to committed B cell response to chronic antigenic stimulation by the infective organism indicating a prolonged duration of infection (Harrus *et al.*, 1997) [16]. Hypoalbuminemia might be attributed to decreased protein intake or anorexia and further peripheral loss to edematous inflammatory fluids as a result of increased vascular permeability consequent to vasculitis (Smitha and Vijaykumar, 2014) [36].

From therapeutic study, in group I ehrlichiosis infected dogs 43.75 per cent of the haemato-biochemical parameters (07/16) did not differ significantly with healthy control dogs with a recovery period of 21 days whereas, in group II dogs treated with single dose of imidocarb, 75.00 per cent of haemato-biochemical parameters (12/16) did not differ significantly

with healthy control dogs with a recovery period of 15 days (Table 3 and Table 4). Doxycycline is semisynthetic lipid soluble tetracycline that are readily absorbed to produce high blood and intracellular concentration to eliminate the infection as Ehrlichia species persists intracellularly. Wells and Rikihisa (1988) [39] cited that doxycycline acted on the ehrlichia organisms by restoring the phagosome- lysosome fusion in infected cells. Faria *et al.* (2010) [11] reported that doxycycline reduced the systemic signs of pro-inflammatory cytokines namely tumour necrosis factor (TNF- alpha), important in acute pathogenesis of Ehrlichiosis by reducing or eliminating the load of parasitemia. Buhles *et al.* (1974) [4]; Neer *et al.* (2002) [27] and Greene (1984) [14] reported successful therapeutic management with drugs like oxytetracycline and doxycycline. Thrombocytopaenia being the major haematological change in canine ehrlichiosis, therefore papaya leaf extract (Caripill®) was given to act as thrombocyte enhancer as reported by many workers (Gammulle *et al.*, 2012; Dharmarathna *et al.*, 2013 and Gowda *et al.*, 2015) [12,7,13]. Kelly (2000) [18] opined that imidocarb dipropionate acted by blocking the entry of inositol, an essential nutrient into the cells containing the parasite, apparently leading to the starvation and inhibiting the infection. There is increasing evidence that immunological mechanisms are involved in the pathogenesis of disease. Thus, immunosuppressive doses of prednisolone in treatment of Canine Monocytic Ehrlichiosis was used. Anaemia being a prominent sign in canine ehrlichiosis, haematinics like dexorange have been given in the affected dogs as ancillary treatment. Therefore, it appears that imidocarb dipropionate is more efficacious in treating canine ehrlichiosis compared to combination of oxytetracycline and doxycycline along with caripill®. Hence, imidocarb dipropionate can be used as first line of treatment against Canine Monocytic Ehrlichiosis which is in accordance with Price and Dolan (1980) [31]; Matthewman *et al.* (1994) [26] and Kumar (2004) [21].

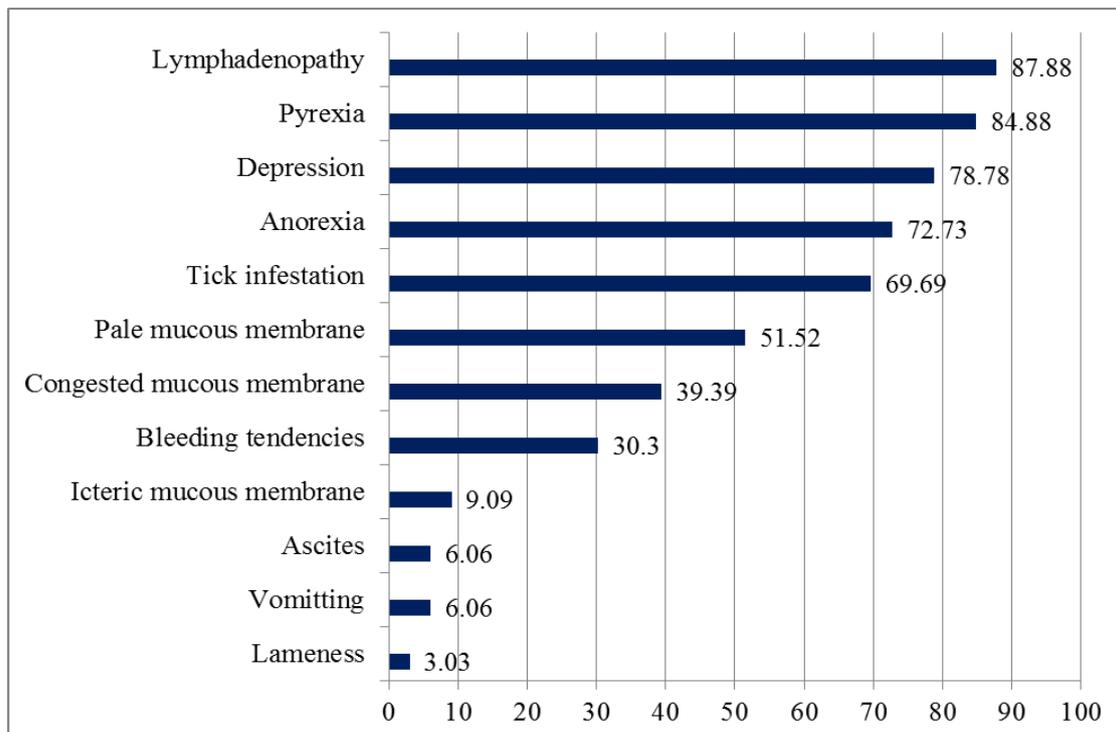


Fig. 1: Frequency of predominant signs as clinical diagnosis of canine ehrlichiosis

Table 1: Haematological changes in ehrlichiosis affected dogs compared to healthy control group

Parameter	Healthy control (0 th day)	Affected dogs (0 th day)
Haemoglobin (g/dL)	14.69 ± 0.19 ^a	8.12 ± 0.96 ^b
TEC (×10 ⁶ /μL)	7.12 ± 0.09 ^a	3.58 ± 0.46 ^b
PCV (%)	44.55 ± 0.89 ^a	25.09 ± 3.01 ^b
Platelets (×10 ³ /μL)	400.75 ± 13.62 ^a	83.50 ± 11.35 ^b
TLC (×10 ³ /μL)	12.47 ± 0.28 ^a	12.04 ± 2.52 ^a
Neutrophils (%)	63.00 ± 0.65 ^a	64.88 ± 4.40 ^a
Lymphocytes (%)	32.63 ± 0.82 ^a	30.75 ± 3.83 ^a
Monocytes (%)	4.13 ± 0.35 ^b	3.13 ± 0.40 ^a
Eosinophils (%)	0.88 ± 0.30 ^a	1.25 ± 0.41 ^a
Basophils (%)	0.48 ± 0.34 ^a	0.45 ± 0.05 ^a

Means bearing different superscripts differ significantly (P≤0.05)

Table 2: Biochemical changes in ehrlichiosis affected dogs compared to healthy control group

Parameter	Healthy control (0 th day)	Affected dogs (0 th day)
BUN (mg/dL)	17.26 ± 0.43 ^a	88.23 ± 4.14 ^b
Creatinine (mg/dL)	0.80 ± 0.03 ^a	2.84 ± 0.26 ^b
ALT (IU/L)	67.22 ± 2.53 ^a	125.85 ± 15.27 ^b
Total protein (g/dL)	6.97 ± 0.09 ^a	5.60 ± 0.57 ^b
Albumin (g/dL)	3.50 ± 0.05 ^a	1.25 ± 0.20 ^b
Globulin (g/dL)	3.47 ± 0.06 ^a	4.35 ± 0.47 ^b
A:G ratio	1.01 ± 0.02 ^a	0.44 ± 0.06 ^b

Means bearing different superscripts differ significantly (P≤0.05)

Table 3: Haematological parameters of ehrlichiosis affected dogs (Group I and II) after treatment in comparison with healthy control dogs

Parameter	Healthy control	Group I affected dogs after treatment (21 st day)	Group II affected dogs after treatment (15 th day)
Haemoglobin (g/dL)	14.69 ± 0.19 ^b	11.11 ± 1.01 ^a	13.35 ± 1.03 ^b
TEC (×10 ⁶ /μL)	7.12 ± 0.09 ^b	5.02 ± 0.57 ^a	5.79 ± 0.38 ^a
PCV (%)	44.55 ± 0.89 ^b	34.89 ± 3.60 ^a	39.12 ± 2.77 ^b
Total Platelet Count (×10 ³ /μL)	400.75 ± 13.62 ^b	240.63 ± 30.64 ^a	295.88 ± 29.05 ^a
TLC (×10 ³ /μL)	12.47 ± 0.28 ^a	12.03 ± 0.89 ^a	13.35 ± 0.77 ^a
Neutrophils (%)	63.00 ± 0.65 ^a	64.00 ± 1.20 ^a	64.38 ± 1.05 ^a
Lymphocytes (%)	32.63 ± 0.82 ^a	30.75 ± 1.29 ^a	30.63 ± 1.45 ^a
Monocytes (%)	4.13 ± 0.35 ^b	4.50 ± 0.19 ^a	4.18 ± 0.32 ^b
Eosinophils (%)	0.88 ± 0.30 ^a	0.75 ± 0.31 ^a	0.63 ± 0.26 ^a

Means bearing different superscripts differ significantly (P≤0.05)

Table 4: Biochemical parameters of ehrlichiosis affected dogs (Group I and II) after treatment in comparison with healthy control dogs

Parameter	Healthy control	Group I after treatment (21 st day)	Group II after Treatment (15 th day)
BUN (mg/dL)	17.26 ± 0.43 ^a	29.88 ± 4.37 ^b	18.65 ± 1.95 ^a
Creatinine (mg/dL)	0.80 ± 0.03 ^a	1.29 ± 0.08 ^b	1.24 ± 0.09 ^b
ALT (IU/L)	67.22 ± 2.53 ^a	69.88 ± 11.31 ^a	77.13 ± 7.66 ^a
Total protein (g/dL)	6.97 ± 0.09 ^b	6.31 ± 0.22 ^a	6.67 ± 0.15 ^b
Albumin (g/dL)	3.50 ± 0.05 ^c	3.21 ± 0.09 ^a	3.07 ± 0.06 ^a
Globulin (g/dL)	3.47 ± 0.06 ^{ab}	3.11 ± 0.21 ^a	3.60 ± 0.14 ^b
A:G ratio	1.01 ± 0.02 ^{ab}	1.07 ± 0.09 ^b	0.86 ± 0.04 ^a

Means bearing different superscripts differ significantly (P≤0.05)

Conclusion

Lymphadenopathy was the most predominant clinical sign followed by pyrexia, depression, bleeding tendencies (epistaxis), icteric mucous membrane, ascites and lameness. Anaemia, thrombocytopaenia, monocytopenia, elevation of BUN, creatinine, ALT along with hypoproteinemia, hypoalbuminemia and hyperglobulinemia were the major haemato-biochemical changes in ehrlichiosis infected dogs. Imidocarb dipropionate was found to be more efficacious in treating canine ehrlichiosis compared to combination of oxytetracycline and doxycycline along with papaya leaf extract (caripill®) in terms of faster recovery and mean treatment days.

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