Original Article

Effeciency of Various Supportive Treatments as A Cure for Anaemia in Cattle with Theileriosis

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Abstract

The purpose of this study was to investigate the efficiency of various supportive treatments on the restoration of anaemia in theileriosis. A total of 20 cattle infected with theileriosis received intramuscularly a single dose of buparvaquone (2.5 mg/kg^{-1} bw) and were divided into 4 equal groups according to the different therapy options: whereas no supportive treatment was applied in group 1, administrations of vitamin B complex, antioxidant vitamins (A, D, E and C), minerals and trace elements were performed in groups 2, 3 and 4, respectively. Haematological parameters, serum concentrations of antioxidant vitamins, minerals and trace elements as well as serum glutathion peroxidase (GSH-Px) and superoxide dismutase (SOD) activities were determined before treatment and 7 days after in infected animals and compared to control values from 10 healthy cattle. In the theileriosis affected cattle, remarkable decreases in haematocrit values, haemoglobinaemia and platelet counts were associated to decreased serum α- / γ-tocopherol, vitamin C, vitamin B_{12}, Ca, Mg, Zn, Na, GSH-Px and SOD levels and to increased sideraemia. The iron concentrations remained elevated and some antioxidants (α- / γ-tocopherol and vitamin C concentrations and GSH-Px and SOD activities) decreased in all treated cattle. Haematocrit values, haemoglobinaemia and vitamin B_{12} concentrations also remained depressed but maximal increases were recorded in cattle receiving vitamins B as supportive therapy (group 2). In parallel, platelet numeration was significantly restored in all groups, but specifically in group 2. On the other hand, the maximal increases in α-tocopherol and Zn concentrations recorded in groups 3 and 4, respectively, were not associated with cure of anaemia. These results show that the most efficient supportive therapy in the cure of anaemia during theileriosis was vitamin B administration.

Keywords: antioxidant vitamins, cattle, trace elements, theileriosis, treatment, vitamin B_{12}

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Introduction

The protozoan parasite, *Theileria annulata,* which is carried out by ticks, may cause one of the important diseases of cattle called tropical theileriosis (Radostits et al., 1994; Ahmed and Mehlhorn, 1999). Its importance is largely observed in grazing cattle in tropical and subtropical climates including Turkey (Yagi et al., 2002; Dumanli et al., 2005; Grewal et al., 2005). Pure -bred and cross-bred cattle (60%) in Turkey are especially threatened by the disease (Sayin et al., 2003; Inci et al., 2007), and if treatment is not applied, the mortality rate is about 62.2% in pure-bred and 40.5% in cross-bred cattle (Inci et al., 2007). Since pure-bred and cross-bred cattle production in Turkey has been increasing in recent years, disease caused by this haemoprotozoan has been attracted by producers and researchers in Turkey (Sayin et al., 2003; Dumanli et al., 2005; Inci et al., 2007). It is detrimental to the production economics due to extensive death losses, decreased milk and meat production, reproductive problems and increasing risk of secondary infections (Zhang, 1990; Radostits et al., 1994; 2005; Inci et al., 2007). For these reasons, choosing the most effective, specific and supportive treatment for the disease gains major importance.

The disease progresses fast in proliferation of lymphoid tissuesive lymphoproliferative disease and is determined by numerous clinical symptoms (Mehta et al., 1988; Keles et al., 2001; Grewal et al., 2005). The main symptom of infected cattle is progressive anaemia because of intraerythrocytic placement of parasites by piroplasms (Shiono et al., 2001; Shiono et al., 2003). A precise mechanism of anaemia has been explained by surface morphological changes in membrane glycolipid and in protein component of RBC, increased osmotic fragility (Shiono et al., 2001; Grewal et al., 2005; Nazifi et al., 2008), abnormal accelerated clearance of damaged RBC by IgG-dependent phagocytosis (Shiono et al., 2003; Shiono et al., 2004), oxidative injuries (Yagi et al., 2002; Shiono et al., 2003; Rezai and Dalir-Naghadeh, 2006), the existence of haemolytic activity in bovine serum having high parasitemia (McHardy, 1990; Nazifi et al., 2008) and cellular immune responses (Ahmed and Mehlhorn, 1999).

Taking into consideration the above mentioned factors related to pathogenesis of anaemia, the most important strategy for treatment is the elimination of the infectious agent with specific treatment and the enhancement of erythropoesis with supportive treatments. If treatment of the diseased animals is not started, they might die within a two week period or recovery could take a very long time (Zhang, 1990). Buparvaquone (BQ), the most effective and safest drug to heal theileria in cattle, has been throughly investigated both *in vitro* and *in vivo* (Dhar et al., 1988; McHardy, 1990; Keles et al., 2001). The drug's recommendation for use is 2.5 mg/kg body weight (bw) injected intramuscularly (IM) for treatment of clinical theileriosis (Dhar et al., 1988; McHardy, 1990; Singh et al., 1993). However, supportive therapy to control the anaemia and pulmonary oedema related to anaemia was found especially beneficial in severe cases (McHardy, 1990; Keles et al., 2001; Altug et al., 2008). The most effective procedure in the supportive treatment for anaemia is blood transfusion (Sandhu et al., 1998; Zhang, 1990), but this is an expensive and difficult procedure; therefore, this method is applied only to very valuable animals (Zhang, 1990). Another option is high density fluid therapy such as 6% dextran (Keles et al., 2001; Temiz et al., 2014). However, this is not often applied by local veterinarians either. Instead, iron, cobalt, liver extract and combination of B complex vitamins have been used in practice for the treatment of anaemia (Zhang, 1990; Dhar et al., 1988; Kumar et al., 1988; Altug et al., 2008). On the other hand, researchers declared high oxidative stress and a strong elevation in lipid peroxidation in the RBC of cattle diagnosed with *Theileria spp,* which is believed to be the most important factor in the pathogenesis of anaemia (Shiono et al., 2003; Grewal et al., 2005; Rezai and Dalir-Naghadeh, 2006). Recently, increased oxidative stress which was detected by the reduction in antioxidant enzymes and vitamin levels in blood of parasitized animals has been observed in *Theileria* infected cattle (Issi and Gul., 2001; Shiono et al., 2001, Nazifi et al., 2008). Furthermore, some researchers have recommended antioxidant vitamins in addition to traditional and/or specific treatment to alleviate the oxidative stress associated with theileriosis and to fill the vitamin storages to avoid consequenced vitamin deficiency in *Theileria* infected cattle (Issi and Gul., 2001; Mahmoud et al., 2006). Although decreased concentrations of serum mineral substances in theileriosis have also been reported by some studies (Yadav and Sharma, 1986; Sandhu et al., 1998; Omer et al., 2003), *Theileria* related anaemia treatments with mineral substances involved in erythropoiesis couldn't not be cited in the literature. For these reasons, in the present study B complex vitamins, antioxidant vitamins and mineral substances were used to determine the effectiveness of the supportive treatment in the *Theileria* related anaemia in addition to BQ.

Materials and Methods

Animal materials and protocol design: This study consisted of 20 heads of cattle (sick animals), exhibiting visible clinical signs of theileriosis, and 10 heads of healthy cattle (control group) from Van city and its suberbs, Turkey. The animals' ages were between 6 months and 9 years and they were from various breeds such as Simmental, Brown Swiss and Holstein. The age ranges of theileria infected animals in each group (n = 5) were as follows; one animal was younger than 1 year of age, one animal was between 1 and 2 years of age, two animals were between 2 and 5 years of age, and one animal was older than 5 years of age. The control animals (n = 10) were 2 animals younger than 1 year of age, two animals between 1 and 2 years of age, four animals between 2 and 5 years of age and 2 animals older than 5 years of age.

The infected animals were identified on the basis of clinical signs, microscopic evaluation and indirect fluorescence antibody tests. Firstly, a clinical examination was conducted on the infected animals for recording specific findings such as fever, swelling of

superficial lymph nodes, paleness or hyperhaemia and petechia on the mucous membranes. For microscopic evaluation, blood smears were obtained by puncturing the ear veins of animals before treatment and after treatment. The blood smears were stained with Giemsa before treatment to reveal piroplasms of *T. annulata* in erythrocytes for diagnosis and for the elimination of other blood parasites (*Babesia* spp and *Anaplasma* spp) and in order to evaluate the treatment efficiency. Mix infections detected with other blood parasites (Anaplasma spp and Babesia spp) in blood smears were excluded from the study. Additionally, circulating anti-*T. annulata* antibodies were determined by an indirect fluorescence test performed at the Parasitology Laboratory (Goddeeris and Chumo, 1982). In this test procedure, 1/20 or over antibody titres were considered as *Theileria* positive.

Then, the 20 infected animals were allotted into 4 equal groups according to mean packed cell volume (PCV) values in order to establish a relative uniformity within each group. For treatment, all infected animals firstly received only once 2.5 mg/kg^{-1} bw IM BQ Butalex® (Cevadif™/Turkey) and then various adjuvant supportive treatments which were vitamin B, vitamins A, D, E and C, and mineral (Zn, Na, Se, Cu, Co and sulphate) complex were given to each group, respectively. (Table 1).

Blood samples and haematological and biochemical analyses: The infected animals were sampled before treatment and 7 days after, whereas the control healthy animals were sampled only once. Blood samples were obtained from the *v. jugularis* puncture and were collected into sterile tubes with and without anti-coagulant. After clotting for 1 hr at room temperature, the blood samples were centrifuged (Rotofix 32®-Hettich/ Germany) at 4 000 g, for 10 s at room temperature and sera were carefully harvested and stored at -20°C until biochemical analysis. Haematological analyses were performed within at most one h after blood sampling by using tubes containing EDTA (Vacutest®-KIMA/ ITALY) as anticoagulant.

Haematological parameters such as haemoglobin (HGB), main corpuscular haemoglobin concentrations (MCHC), packed cell volume (PCV), white blood cell counts (WBC), platelet counts (PLT), peripheral blood polymorphonuclear leukocytes counts (PBPL), peripheral blood mononuclear leukocytes counts (PBML) and their percentages were determined by using QBCvetautoreader® cell counter (IDEXX / USA).

Serum sodium, potassium and chloride concentrations were measured using ion selective device (ISE®-Medica/USA). Serum mineral substance concentrations including calcium (Ca), magnesium (Mg), copper (Cu), iron (Fe) and zinc (Zn) were analysed by using atomic absorption spectrophotometer (Solar AA Spectrometers®-Thermo Elk. Co./UK). Antioxidant vitamins such as retinol, retinol acetate, α-tocopherol, α-tocopherol acetate and γ-tocopherol were determined using liquid chromotography equipment (HPLC 1100®-Agilent Technologies/USA) and vitamin C was determined by spectrophotometry (Photometer 5010®-Boehringer-Mannheim/Germany) according to references (Omaye et al., 1979; Zaspel and Csallany, 1983; Miller and Yang, 1985). The antioxidant enzymes, superoxide dismutase (SOD) and glutathione peroxidase (GSPX) were determined by commercial kits (RANSOD®-SD125, RANSEL®-RS505/ Randox/UK, respectively) using spectrophotometer (Photometer 5010® Boehringer-Mannheim/Germany). Serum vitamin B_{12} concentrations were determined by immunoassay apparatus using a commercial kit (Elecsys 2010®-Roche, Boehringer-Mannheim/Germany).

Statistical analysis: Data was not normally distributed. Therefore, non-parametric Mann Whitney U test was performed to compare two independent group mean ranks (Control vs total infected group). Wilcoxon test was used to see if there was a difference

Table 1. Supportive vitamin and/or mineral treatment options applied to different groups of *T. annulata* infected cattle (n = 5 in each group) in addition to BQ Butalex® (Cevadif™/Turkey) (2.5 mg/kg^{-1} bw, IM)

Groups	Options	Modalities (drugs and doses)
Group 1	**No supportive treatment**	-
Group 2	**Vitamins B**	Berovit B_{12}® (Cevadif İlaç A.Ş, Turkey)[1] 1 mL/20 kg^{-1} bw IM for 5 days
Group 3	**Vitamins ADE + C**	Ademin® (Cevadif İlaç A.Ş, Turkey)[2] 0.1 mL/10 kg^{-1} bw IM once only İnjacom C® (Cevadif İlaç A.Ş, Turkey)[3] 0.5 mL/10 kg^{-1} bw for IM 5 days
Group 4	**Minerals**	Zinkosel® (Provet, Turkey)[4] 1 tablet/ 100 kg^{-1}bw PO for 2 days

[1]Berovit B_{12} contains per mL: 5 mg vitamin B_1, 2 mg vitamin B_2, 2 mg vitamin B_6, 4 µg vitamin B_{12}, 20 mg nicotinamid and 10 mg d-panthenol; [2]Ademin contains per mL: 500 000 IU vitamin A, 75 000 IU vitamin D_3 and 50 mg vitamin E; [3]İnjacom C contains per mL 200 mg vitamin C; [4]Zincosel contains per tablet: 0.5 mg α-tocopherol acetate, 10 mg zinc sulphate, 2.5 mg sodium selenite, 10 mg copper sulphate and 12.5 mg cobalt sulphate

between two dependent group means (before and after treatments). Kruskal Wallis test was used to see if there was a difference among group means (5 groups including control group). If the Kruskal Wallis test detected a difference among groups then the groups were compared in pairs using Mann Whitney U test. Statistical significance was tested at $p<0.05$ level. For this purpose, the SPSS 16.0 software was used. All data were expressed as means ± standard error of the means (SEM).

Results

Clinical findings: The main clinical signs observed in the cattle with theileriosis before treatment were a marked fever, increased heart and respiration rates, swelling of prescapular and subiliac lymph nodes, ruminal atony, inappatence and weakness. There were also common paleness or hyperhaemia and dot type bleedings on the mucous membranes and dyspnoea and coughing developed as a result of pulmoner oedema. By contrast, the observed clinical findings in all the groups were extensively reduced equally, and/or even disappeared after treatment.

Haematological findings: The haematological findings obtained from the cattle with theileriosis and the healthy control cattle are given in Table 2.

Before treatment, haemoglobinemia, haematocrit values and platelet counts were dramatically depressed in all infected animals ($p < 0.001$) whereas the MCHC and mean leukocyte parameters were not significantly altered.

After treatment with or without supportive measures, the platelet numerations were markedly improved compared to pre-treatment values and were even slightly higher than the control values in all groups of infected cows ($p < 0.001$ for the overall group of infected cattle, $p < 0.01$ for groups 1, 2, 3 and 4). WBC also tended to increase in all infected cattle whatever the received treatment was. By contrast, although haemoglobinemia and PCV values were observed to increase after treatment compared to the initial values, they remained lower than the control group values ($p < 0.001$ for HGB; $p < 0.01$ for PCV). However, when the cows received vitamins B in addition to BQ (group 2), these 2 erythrocyte parameters dramatically increased compared to the pre-treatment values ($p < 0.05$) and the increase in platelet counts was maximal (223.4%) compared to the other groups (between 70.6% and 128.0%).

Serum vitamin concentrations and antioxidant enzyme activities: The serum vitamin concentrations and antioxidant enzyme activities of infected animals are given in Table 3. In the diseased animals before

Table 2. Haematological parameters in control healthy cattle and in cattle with theileriosis before and after treatment with BQ Butalex® (Cevadif™/Turkey) (2.5 mg/kg^{-1} bw, IM) and various supportive adjuvant treatments (group 1: absent; group 2: vitamin B; group 3: vitamins A, D, E and C; group 4: minerals). Results are expressed as mean ± SEM (standard error of the mean).

Parameters		Controls (n = 10)	Cattle with theileriosis (n = 20)				
			Total (n = 20)	Group 1 (n = 5)	Group 2 (n = 5)	Group 3 (n = 5)	Group 4 (n = 5)
PCV (%)	Before T.	37.76 ± 2.64^{a}	22.08 ± 1.92^{d}	21.97 ± 3.93^{d}	23.22 ± 2.42^{d}	22.12 ± 4.92^{d}	21.01 ± 4.57^{d}
	After T.		24.74 ± 1.53^{c}	23.30 ± 2.97^{cd}	30.07 ± 2.31^{b}	23.37 ± 2.20^{cd}	22.23 ± 3.27^{cd}
Hb (g/L)	Before T.	129.6 ± 7.4^{a}	74.0 ± 6.7^{b}	75.5 ± 13.5^{b}	78.2 ± 10.7^{b}	76.2 ± 19.1^{b}	66.2 ± 13.5^{b}
	After T.		81.1 ± 5.4^{b}	76.2 ± 10.8^{b}	99.0 ± 9.5^{c}	75.7 ± 10.0^{b}	73.7 ± 11.4^{b}
MCHC (g/L)	Before T.	345.2 ± 9.0	335.7 ± 5.0	342.5 ± 8.8	345.5 ± 7.2	340.6 ± 13.8	314.5 ± 8.5
	After T.		323.5 ± 3.6	326.2 ± 9.3	321.7 ± 3.4	327.6 ± 7.2	318.5 ± 9.4
WBC (10^9/L)	Before T.	11.14 ± 0.90	10.03 ± 0.95	8.85 ± 1.67	10.97 ± 1.40	11.07 ± 1.88	9.22 ± 1.27
	After T.		11.31 ± 1.24	11.17 ± 1.08	10.45 ± 1.36	11.85 ± 1.59	11.76 ± 1.37
PBPL (10^9/L)	Before T.	2.88 ± 0.61	2.69 ± 0.54	2.70 ± 0.73	2.00 ± 0.23	2.97 ± 1.37	3.12 ± 1.16
	After T.		3.50 ± 0.66	4.70 ± 2.18	2.45 ± 0.86	2.95 ± 0.84	3.93 ± 0.61
PBPL (%)	Before T.	24.80 ± 4.09	27.66 ± 3.79	34.00 ± 10.00	19.13 ± 1.49	23.00 ± 7.83	34.50 ± 7.57
	After T.		30.11 ± 4.91	39.00 ± 15.30	23.44 ± 9.86	26.75 ± 4.69	31.25 ± 5.03
PBML (10^9/L)	Before T.	8.26 ± 0.47	7.33 ± 0.77	6.15 ± 1.82	8.97 ± 1.20	8.10 ± 1.32	6.10 ± 0.76
	After T.		7.68 ± 0.68	6.47 ± 1.61	8.00 ± 1.47	7.40 ± 0.91	8.85 ± 1.74
PBML (%)	Before T.	75.20 ± 4.09	72.34 ± 3.79	66.00 ± 10.00	80.87 ± 1.49	77.00 ± 7.83	65.50 ± 7.57
	After T.		69.89 ± 4.91	61.00 ± 15.30	76.56 ± 9.86	73.25 ± 4.69	68.75 ± 5.03
PLT (10^9/L)	Before T.	543.0 ± 19.1^{a}	299.7 ± 42.5^{b}	331.5 ± 52.0^{b}	209.0 ± 46.7^{b}	377.2 ± 52.2^{b}	281.2 ± 59.1^{b}
	After T.		640.4 ± 48.3^{a}	565.5 ± 39.8^{a}	676.0 ± 52.6^{a}	679.0 ± 48.1^{a}	641.0 ± 45.9^{a}

T: Treatment; PCV: Packed cell volume (%); Hb: Haemoglobinemia; WBC: White blood cells; PBPL: Peripheral blood polymorphonuclear leukocytes; PBML: peripheral blood mononuclear leukocytes; PLT: Platelet
Different superscripts a,b,c,d for a given parameter indicate significant differences ($p < 0.05$ or more)

treatment, the α-tocopherol and α-tocopherol actetate, γ-tocopherol, vitamin C and vitamin B_{12} concentrations and the GSH-Px and SOD activities were significantly lowered compared to the control values ($p < 0.05$ for α- and γ-tocopherol, SOD; $p < 0.01$ for α-tocopherol acetate GSH-Px; $p < 0.001$ for vitamins C and B_{12}). Furthermore, some of these parameters (vitamin B_{12}, GSH-Px and SOD) continued to decrease even after treatment. In particular, the serum vitamin B12 concentrations after treatment were significantly depressed compared to the initial pre-treatment values in all infected groups ($p < 0.05$) except in group 2 (BQ + vitamin B as supportive treatment), in which this parameter was significantly increased ($p < 0.05$). Besides, the retinol acetate concentrations after treatment were significantly increased compared to the initial values ($p < 0.05$) in this group, whereas no significant treatment effect was evidenced in the other 3 groups even in group 3, in which the cows received vitamins A, D, E and C supportive treatment. On the other hand, the cows from group 3 (treated with BQ and vitamins A, D, E and C as supportive treatment) exhibited significantly higher concentrations of serum α-tocopherol acetate and α-tocopherol after treatment than in the other groups (group 3 vs. groups 1, 2 or 4: $p < 0.05$, for α-tocopherol acetate and group 3 vs. group 1: $p < 0.05$ for α-tocopherol).

Serum mineral and trace element concentrations: Some serum mineral and trace element concentrations of the infected animals are given in Table 4. It was observed that the Ca, Mg, Zn and Na concentrations were significantly depressed in the cattle with theileriosis before treatment compared to the control values ($p < 0.05$ for Mg and Zn, $p < 0.01$ for Ca, $p < 0.001$ for Na), whereas the sideremia was markedly increased ($p < 0.05$) and the mineral (Na, K and Cl) and Cu concentrations did not significantly differ between the infected and control animals, although they tended to slightly decreased. The BQ treatment with or without vitamin/mineral concomittant administrations significantly restored calcaemia ($p < 0.01$), magnesiaemia ($p < 0.05$), zincaemia ($p < 0.05$) and natraemia ($p < 0.05$) in all infected cows. In parallel, the iron concentrations also declined after treatment but they remained significantly elevated compared to the control values ($p < 0.05$). The increase in Mg concentrations observed after treatment was significant in groups 1 (no supportive treatment) and 4 (with mineral supply) and adjuvant mineral administration induced maximal variations in zincaemia (+ 132.0% in group 4, +13.6% in group 3, 11.2% in group 2 and -7.0% in group 1).

Table 3. Serum vitamin concentrations and antioxidant enzyme activities in control healthy cattle and in cattle with theileriosis before and after treatment with BQ Butalex® (Cevadif™/Turkey) (2,5 mg/kg^{-1} bw, IM) and various supportive adjuvant treatments (group 1: absent; group 2: vitamin B; group 3: vitamins A,D, E and C; group 4: minerals). Results are expressed as mean ± SEM (standard error of the mean).

Parameters		Controls (n = 10)	Cattle with theileriosis (n = 20)				
			Total (n = 20)	Group 1 (n = 5)	Group 2 (n = 5)	Group 3 (n = 5)	Group 4 (n = 5)
Retinol (mg/L)	Before T.	0.72 ± 0.05	0.65 ± 0.04	0.67 ± 0.05	0.53 ± 0.13	0.72 ± 0.04	0.66 ± 0.10
	After T.		0.68 ± 0.07	0.63 ± 0.17	0.65 ± 0.20	0.75 ± 0.06	0.69 ± 0.19
Retinol Ac. (mg/L)	Before T.	0.62 ± 0.04	0.57 ± 0.04	0.55 ± 0.07	0.53 ± 0.04^{a}	0.60 ± 0.08	0.59 ± 0.02
	After T.		0.55 ± 0.05	0.45 ± 0.12	0.64 ± 0.05^{b}	0.64 ± 0.06	0.49 ± 0.11
α-Tocopherol (mg/L)	Before T.	1.71 ± 0.10^{a}	1.18 ± 0.13^{c}	1.09 ± 0.38^{c}	1.15 ± 0.27^{c}	1.27 ± 0.15^{c}	1.23 ± 0.18^{c}
	After T.		1.12 ± 0.13^{bc}	0.78 ± 0.02^{c}	1.27 ± 0.29^{bc}	1.40 ± 0.17^{b}	1.02 ± 0.10^{bc}
α-Tocopherol Ac. (mg/L)	Before T.	1.44 ± 0.10^{a}	0.74 ± 0.14^{c}	0.71 ± 0.39^{c}	0.62 ± 0.29^{cd}	0.84 ± 0.26^{bc}	0.78 ± 0.12^{c}
	After T.		0.68 ± 0.10^{cd}	0.34 ± 0.26^{d}	0.66 ± 0.08^{cd}	1.07 ± 0.21^{ab}	0.67 ± 0.09^{cd}
γ-tocopherol (mg/L)	Before T.	0.80 ± 0.04^{a}	0.58 ± 0.06^{b}	0.60 ± 0.11^{b}	0.57 ± 0.08^{b}	0.66 ± 0.15^{b}	0.51 ± 0.08^{b}
	After T.		0.55 ± 0.06^{b}	0.50 ± 0.11^{b}	0.57 ± 0.10^{b}	0.68 ± 0.12^{ab}	0.47 ± 0.08^{b}
Vitamin C (mg/L)	Before T.	6.6 ± 0.6^{a}	2.0 ± 0.2^{b}	1.6 ± 0.3^{b}	1.9 ± 0.2^{b}	2.4 ± 0.3^{b}	2.3 ± 0.2^{b}
	After T.		2.3 ± 0.2^{c}	1.9 ± 0.5^{c}	2.0 ± 0.3^{bc}	2.5 ± 0.3^{bc}	2.7 ± 0.4^{bc}
Vitamin B_{12} (ng/L)	Before T.	553.6 ± 55.4^{a}	306.1 ± 31.1^{bc}	270.2 ± 48.0^{bc}	208.0 ± 36.1^{c}	374.3 ± 62.6^{b}	371.7 ± 72.3^{b}
	After T.		259.5 ± 33.9^{c}	155.6 ± 35.8^{d}	388.4 ± 52.0^{b}	250.2 ± 73.4^{c}	243.9 ± 37.3^{c}
GSH-Px (U/g Hb)	Before T.	53.3 ± 5.57^{a}	35.1 ± 4.14^{b}	39.7 ± 4.94^{b}	23.6 ± 6.86^{bc}	35.5 ± 9.91^{b}	41.8 ± 9.10^{b}
	After T.		28.1 ± 2.09^{c}	27.1 ± 3.87^{bc}	25.5 ± 5.00^{bc}	28.7 ± 4.76^{bc}	31.2 ± 4.38^{bc}
SOD (10^3U/g Hb)	Before T.	2.07 ± 0.24^{a}	1.60 ± 0.14^{b}	1.55 ± 0.32^{b}	1.30 ± 0.17^{bc}	1.43 ± 0.32^{b}	2.10 ± 0.31^{ab}
	After T.		1.33 ± 0.16^{c}	1.38 ± 0.22^{bc}	1.10 ± 0.08^{c}	1.29 ± 0.14^{bc}	1.56 ± 0.28^{abc}

T: Treatment; Ac.: Acetate; Hb: Haemoglobinemia; GSH-Px: glutathione peroxidase; SOD: superoxide dismutase
Different superscripts a,b,c,d for a given parameter indicate significant differences ($p < 0.05$ or more)

Discussion

The aim of this study was to determine the effeciency of various supportive treatments in anaemic cattle having theileriosis. To the best of our knowledge, there has been no research presenting the theileriosis and supportive treatment options, including B complex vitamins, antioxidant vitamins or mineral substances plus BQ. In the present study, it was shown that the most efficient treatment in restoration of anaemia in theileriosis was the association of BQ with vitamins B complex including vitamin B_{12}.

The clinical signs of theileriosis before treatment in the present study were similar to those reported earlier (Mehta et al., 1988; Keles et al., 2001; Omer et al., 2003). However, the observed clinical findings after BQ therapy almost completely disappeared or largely decreased in all infected groups in the present study. This result was similar to that reported by other researchers concerning treatment by BQ of *T. annulata* infections (McHardy, 1990; Singh et al., 1993; Dhar et al., 1988;). Despite the fact that various symptoms have been reported in theileriosis (Mehta et al., 1988; Keles et al., 2001; Omer et al., 2003), the main clinical sign in cattle is progressive anaemia (Shiono et al., 2001; Shiono et al., 2003; Temiz et al., 2014). Therefore, in evaluation of the recovery status from this disease after treatment, RBC counts and/or related paremeters such as PCV and haemoglobinemia were commonly used (Temiz et al., 2014). In this study, significant decreases in PCV values and haemoglobinemia compared to the control group were observed before treatment (Table 2) and these results were in agreement with previous reports (Maxie et al., 1982; Sandhu et al., 1998, Singh et al., 2001). However, these 2 parameters were slightly increased after treatment, but the corresponding relative variations were not significant before and after treatment except in group 2, in which the cows additionally received vitamin B ($p < 0.05$). This situation may be explained by the erythropoietic effect which possibly occurred after B complex vitamin administration (especially in group 2). Serum vitamin B_{12} concentrations decreased significantly even after treatment in the infected groups 1, 3 and 4 but not in group 2, to which B complex vitamin was applied (Table 3). This situation showed that the utilization of vitamin B_{12} increased according to the severity of the anaemia, and consequently the serum vitamin B_{12} concentrations decreased in the infected animals. After parenteral vitamin B_{12} application in addition to BQ, the consumption of the circulating vitamin B_{12} was stopped and even a mild increase in the serum vitamin concentrations was seen in group 2 (Table 3). These results showed that vitamin B_{12} enhanced erythropoiesis. These findings are compatible with the results of Dhar et al. (1988), who showed that administration of hematinics (including B complex vitamin) plus BQ halted the decreases in haematocrit and haemoglobinaemia more quickly than treatment with BQ alone. Moreover, Keen and Graham (1989) suggested that decreased vitamin B_{12} concentrations in animals might be derived from the relative inefficiency

Table 4. Serum mineral and trace element concentrations in control healthy cattle and in cattle with theileriosis before and after treatment with BQ Butalex® (Cevadif™/Turkey) (2.5 mg/kg^{-1} bw, IM) and various supportive adjuvant treatments (group 1: absent; group 2: vitamin B; group 3: vitamins A, D, E and C; group 4: minerals). Results are expressed as mean ± SEM (standard error of the mean).

Parameters		Controls (n = 10)	Cattle with theileriosis (n = 20)				
			Total (n = 20)	Group 1 (n = 5)	Group 2 (n = 5)	Group 3 (n = 5)	Group 4 (n = 5)
Ca (mmol/L)	Before T.	2.54 ± 0.07^{a}	2.26 ± 0.05^{b}	2.19 ± 0.05^{b}	2.25 ± 0.15^{ab}	2.28 ± 0.12^{ab}	2.32 ± 0.09^{ab}
	After T.		2.47 ± 0.04^{a}	2.32 ± 0.05^{ab}	2.51 ± 0.08^{a}	2.55 ± 0.11^{a}	2.51 ± 0.05^{a}
Mg (mmol/L)	Before T.	0.79 ± 0.03^{a}	0.69 ± 0.03^{b}	0.66 ± 0.02^{b}	0.76 ± 0.12^{a}	0.65 ± 0.06^{b}	0.69 ± 0.07^{b}
	After T.		0.79 ± 0.03^{a}	0.79 ± 0.04^{a}	0.76 ± 0.08^{a}	0.75 ± 0.06^{ab}	0.84 ± 0.06^{a}
Cu (µmol/L)	Before T.	15.3 ± 0.8	13.4 ± 1.3	11.6 ± 2.4	16.8 ± 4.1	11.6 ± 2.8	13.2 ± 1.9
	After T.		14.6 ± 1.4	17.6 ± 2.2	17.3 ± 3.3	11.2 ± 3.0	12.4 ± 0.8
Fe (µmol/L)	Before T.	19.3 ± 2.7^{a}	36.5 ± 6.4^{b}	48.7 ± 14.5^{b}	29.4 ± 5.6^{ab}	32.6 ± 4.1^{ab}	35.5 ± 18.8^{b}
	After T.		33.7 ± 6.3^{b}	29.4 ± 5.7^{ab}	30.3 ± 8.6^{ab}	35.6 ± 6.6^{b}	39.6 ± 19.9^{b}
Zn (µmol/L)	Before T.	9.2 ± 0.6^{a}	7.2 ± 0.6^{b}	8.1 ± 1.2^{ab}	8.9 ± 0.8^{ab}	6.6 ± 1.4^{b}	5.0 ± 0.8^{b}
	After T.		9.2 ± 0.9^{a}	7.5 ± 0.9^{ab}	9.9 ± 1.4^{a}	7.5 ± 1.7^{ab}	11.6 ± 2.4^{a}
Na (mEq/L)	Before T.	140.9 ± 1.2^{a}	134.2 ± 1.1^{b}	133.6 ± 1.5^{b}	131.2 ± 3.7^{b}	136.1 ± 1.4^{b}	136.0 ± 1.1^{b}
	After T.		137.2 ± 1.1^{c}	138.9 ± 2.6^{abc}	135.9 ± 0.9^{c}	138.7 ± 2.5^{abc}	135.4 ± 2.8^{bc}
K (mEq/L)	Before T.	4.29 ± 0.11	4.09 ± 0.07	4.20 ± 0.17	4.11 ± 0.13	4.08 ± 0.18	3.98 ± 0.16
	After T.		4.40 ± 0.13	4.40 ± 0.20	4.77 ± 0.17	4.18 ± 0.22	4.26 ± 0.23
Cl (mEq/L)	Before T.	103.0 ± 1.2	100.4 ± 0.8	99.2 ± 1.4	100.1 ± 0.7	100.6 ± 2.4	101.9 ± 1.9
	After T.		101.7 ± 1.2	103.8 ± 3.5	101.5 ± 1.8	100.7 ± 1.5	101.0 ± 3.1

T: Treatment

Different superscripts a,b,c,d for a given parameter indicate significant differences ($p < 0.05$ or more)

of vitamin B_{12} production in the rumen which had poor absorption (due to increased iron), low transport in the ileum (due to decreased protein transport and intrinsic factors) and increased consumption for erythropoiesis.

Thrombocytopenia and coagulopathy are characteristics of haematological findings in theileriosis (Maxıe et al., 1982; Singh et al., 2001). In accordance, platelet populations were dramatically depressed in all cattle with theileriosis before treatment in the present study and PLT counts increased in all infected groups after treatment. Again, this increase was maximal in group 2 compared to the other groups (Table 2). The variation in the thrombocyte population would be considered as a prognosis marker of response to treatment in theileriosis.

Leukopenia (Maxıe et al., 1982; Sandhu et al., 1998) or even leukocytosis (Sandhu et al., 1998, Singh et al., 2001) were reported in theileriosis by different workers. Moreover, initially or at the acute phase of theileriosis, leukocytosis were observed followed by a significant leukopenia in the terminal or latent stages (Sandhu et al., 1998). In the present study, WBC counts, differential leukocyte counts and ratios did not change (Table 2). This situation may be explained by the presence of different infection periods (mild, moderate, severe) of animals in each groups used in the present study.

Oxidative damage in erythrocytes due to oxidative stress and lipid peroxidation may be strongly involved in the consequences of anaemia in theileriosis (Yagi et al., 2002; Shiono et al., 2003; Nazifi et al., 2008). Moreover, the activities of antioxidant enzymes in RBC from affected cattle were found to decrease as the severity of anaemia and parasitemia increase (Rezai and Dalir-Naghadeh, 2006). Furthermore, it has been reported that an increase in oxidative stress leads to a decrease in antioxidant vitamins such as vitamins E and C (Yadav and Sharma, 1986; Issi and Gul., 2001; Shiono et al., 2001), whereas an increase in oxidative stress leads to an increase (Grewal et al., 2005), decrease (Ozan et al., 1999; Rezai and Dalir-Naghadeh, 2006; Nazifi et al., 2008;) and no changes (Nazıroglu et al., 1999; Grewal et al., 2005) in antioxidant enzyme (such as GSH-Px and SOD) activities in infected animals. In agreement with the majority of reports (Nazıroglu et al., 1999; Issi and Gul., 2001; Grewal et al., 2005; Rezai and Dalir-Naghadeh, 2006; Nazifi et al., 2008), the antioxidant vitamin concentrations and the antioxidant enzyme activities in the present study were found to be depressed in infected cattle before treatment compared to the healthy control animals (Table 3). Furthermore, the activities of GSH-Px and SOD continued to decrease even after treatment in all infected animals (Table 3), particularly in group 2 (additionally treated with vitamin B), whereas the erythrocyte parameters (haematocrit and haemoglobinaemia) were increased (Table 2). These findings are in accordance with Nazıroglu et al. (1999), who reported that increased lipid peroxidation was also determined in cattle treated with BQ. These authors speculated that BQ treatment could induce formation of free radicals (Nazıroglu et al., 1999). In this study, serum vitamin A concentrations did not change except in the group 2 as early seen in the study of Nazıroglu et al. (1999). In this group, the retinol acetate concentrations were significantly enhanced after treatment; this situation may be due to the recovery of ruminal functions and appetite after treatment. Although the application of antioxidant vitamins such as vitamins A, C and E for the supportive treatment of theileriosis caused an increase in serum vitamin E concentrations in group 3, it did not help in the recovery of the haematological parameters, especially for PCV and haemoglobinaemia.

Significant decreases in serum Ca, Mg, Zn and Na concentrations were recorded in the cattle with theileriosis before treatment compared to the healthy control animals ($p < 0.001$ to 0.05) whereas serum Fe concentrations showed significant increases before and after treatment ($p < 0.05$) in the present study (Table 4). Decreases in Ca (Singh et al., 2001; Omer et al., 2003), Mg (Yadav and Sharma, 1986; Omer et al., 2003), Zn (Kumar and Malik, 1999) and Na (Hasanpour et al., 2008; Temiz et al., 2014) concentrations have previously been reported in theileriosis. It was also observed that no significant differences in calcemia, magnesiemia and zincaemia were evidenced between the healthy and treated infected cows. Moreover, these 3 parameters did not significantly differ between the groups after treatment although the increase in zincaemia observed after treatment in infected cattle was significantly more pronounced in group 4, which received minerals and trace elements as supportive treatment, than in the other groups (Table 4). In addition, there was no correlation with zincaemia and haematocrit values or haemoglobinaemia (which are important markers in the determination of anaemia), suggesting that the administration of mineral substances for supportive therapy in theileriosis is not effective in curing anaemia. The decreased serum Na levels in the present study may be explained by Hasanpour et al. (2008) notifications, who reported that the decrease in natraemia might be due to anorexia, hypoproteinemia, malfunction of intestine and renal damage in theileriosis.

Some researchers have observed a decrease (Kumar and Malik, 1999; Omer et al., 2003), whereas others reported an increase (Watanabe et al., 1998) in sideraemia in theileriosis. The increased serum Fe concentrations in the present study were compatible with Watanabe et al. (1998), in which a marked increase in sidaeremia and transferrin saturation were detected in anaemic cattle infected with *T. sergenti* during the development of anaemia.

In the present study, only the administration of minerals and trace elements (including cobalt) as supportive treatment (group 4) failed to improve the erythrocyte parameters (PCV and haemoglobinaemia) and vitamin B_{12} concentrations. Katsuoka et al. (1983) demonstrated that cobalt administration during hypoxia stimulated the kidney erythropoietin production more efficiently than the two potent erythropoietic stimuli alone, suggesting a potentiating effect of cobalt on the renal action of hypoxia. Nevertheless, although the development of anaemia in theileriosis may cause hypoxia because of respiratory distress (dyspnoea, nasal discharge and cough due to pulmonar oedema) (Mehta et al., 1988; Singh et al., 2001; Omer et al., 2003), mineral supportive therapy did not significantly corrected anaemia in the current

study. In contrast to group 4, the parenteral application of vitamin B complex containing vitamin B_{12} (group 2) caused a marked improvement of the erythrocyte parameters and restoration of vitamin B_{12} concentrations. It is probable that vitamin B_{12} administration promoted the intensity of erythropoiesis already stimulated by hypoxia and erythropoietin production as the cobalt promoting effects described by Katsuoka et al. (1983). This situation in group 4 may be explained by the inefficiency of vitamin B_{12} production in the rumen, poor absorption of vitamin B_{12} by abnormal ileal mucosa or decreased intrinsic factor synthesis reported by Keen and Graham (1989). The ruminal atony and inappatence observed in the present study could be the reason for the low production of vitamin B_{12}.

In conclusion, it was determined that the most important therapy option in the supportive treatment plus BQ for restoration of anaemia in theileriosis was the use of vitamin B complex containing vitamin B_{12}, whereas the administrations of antioxidant vitamins (A, E and C) or minerals/trace elements (including cobalt) for supportive therapy in theileriosis were not effective. Furthermore, platelet counts dramatically depressed in diseased animals were markedly increased after treatment and the thrombocyte numeration may be used as a prognosis marker in addition to haematocrit and haemoglobinaemia in theileriosis. Further studies should focus on relationships between vitamin B_{12}, degree of hypoxia and erythropoiesis and various doses of vitamin B_{12} should be studied to elucidate the mechanisms of its effects on erythropoiesis.

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บทคัดย่อ

ประสิทธิภาพของการรักษาแบบประคับประคองในหลายรูปแบบ เพื่อการรักษาภาวะโลหิตจางในโคที่เป็นโรคไทเลอริโอซิส

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วัตถุประสงค์ของการศึกษานี้เพื่อวิจัยประสิทธิภาพของการรักษาแบบประคับประคองในหลายรูปแบบในการฟื้นฟูภาวะโลหิตจางในโรคไทเลอริโอซิส โคจำนวนทั้งสิ้น 20 ตัวที่เป็นโรคไทเลอริโอซิสได้รับ buparvaquone (2.5 มก./กกของน้ำหนักตัว .) เพียงครั้งเดียวทางกล้ามเนื้อ และถูกแบ่งเป็น 4 กลุ่มจำนวนเท่ากัน ตามรูปแบบการรักษาที่แตกต่างกัน กลุ่มที่ 1 ไม่ได้รับการรักษาแบบประคับประคอง กลุ่มที่ 2 ได้รับวิตามิน B complex กลุ่มที่ 3 ได้รับวิตามินที่เป็นสารต้านอนุมูลอิสระ (A, D, E และ C) กลุ่มที่ 3 ได้รับแร่ธาตุและแร่ธาตุที่พบน้อยแต่จำเป็น ตัวชี้วัดทางโลหิตวิทยา ความเข้มข้นของวิตามินที่เป็นชนิดต้านอนุมูลอิสระ ของแร่ธาตุ และแร่ธาตุที่พบน้อยแต่จำเป็นในน้ำเลือด รวมทั้งการทำงานของ glutathione peroxidase (GSH-Px) และ superoxide dismutase (SOD) ได้ถูกวัดในสัตว์ที่ติดเชื้อก่อนการรักษาและ 7 วันหลังจากการรักษา แล้วนำมาเปรียบเทียบกับค่าจากกลุ่มควบคุมซึ่งเป็นโคจำนวน 10 ตัวที่มีสุขภาพดี ในกลุ่มโคที่เป็นโรคไทเลอริ-โอซิส ระดับที่ต่ำลงอย่างชัดเจนของค่าเม็ดเลือดแดงอัดแน่น ภาวะฮีโมโกลบินในเลือด และจำนวนเกล็ดเลือด มีความสัมพันธ์กับระดับที่ลดลงในน้ำเลือดของ α-/γ- tocopherol, วิตามิน C, วิตามิน B12, แคลเซียม แมกเนเซียม สังกะสี โซเดียม GSH-Px และ SOD และมีความสัมพันธ์กับการเพิ่มขึ้นของธาตุเหล็กในกระแสเลือด ความเข้มข้นของธาตุเหล็กยังคงอยู่ในระดับสูง และสารต้านอนุมูลอิสระบางชนิด (ความเข้มข้นของ α-/γ- tocopherol และวิตามิน C และการทำงานของ GSH-Px และ SOD) ลดลงในโคที่ได้รับการรักษา ระดับของค่าเม็ดเลือดแดงอัดแน่น ภาวะมีฮีโมโกลบินในเลือดและความเข้มข้นของวิตามิน B12 ยังคงมีค่าต่ำ แต่การเพิ่มขึ้นสู่ระดับสูงสุดถูกบันทึกได้ในโคที่ได้รับวิตามิน B เป็นการรักษาแบบประคับประคอง (กลุ่มที่ 2) ในทำนองเดียวกัน จำนวนของเกล็ดเลือดถูกฟื้นฟูสภาพอย่างมีนัยสำคัญในทุกกลุ่ม แต่มีความจำเพาะในกลุ่มที่ 2 ในทางกลับกัน พบการเพิ่มขึ้นอย่างสูงสุดของความเข้มข้นของ α-tocopherol และสังกะสีในกลุ่มที่ 3 และ 4 ตามลำดับ ซึ่งไม่มีความสัมพันธ์กับการรักษาภาวะโลหิตจาง ผลการศึกษาเหล่านี้แสดงให้เห็นว่าการรักษาประคับประคองส่วนใหญ่ที่มีประสิทธิภาพในการรักษาภาวะโลหิตจางขณะที่เป็นโรคไทเลอริโลซิส คือ การให้วิตามิน B

คำสำคัญ: วิตามินที่เป็นสารต้านอนุมูลอิสระ โค แร่ธาตุที่พบน้อย โรคไทเลอริโอซิส การรักษา วิตามิน B12

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