

RED AND WHITE BLOOD PROFILE IN RABBITS AFTER EXPERIMENTALLY INDUCED INFECTION WITH SPORULATED OOCYSTS OF *EIMERIA STIEDAE*

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ABSTRACT

The aim of this study was to identify changes in parameters of blood count in rabbits with experimentally induced liver coccidiosis. In the experiment were used 12 New Zealand White rabbits, divided into experimental and control groups, each consisting of 6 animals. The animals from experimental group were orally infected by 50 000 sporulated *E. stiedae* oocysts. Blood samples were drawn from all rabbits before (0 hour) and 6, 24, 48 hours, and also 7, 14, 21, 28 days after infection. There were established significant differences ($P < 0.05$) in the parameters of the blood count in the experimental group, compared to the control group.

Key words: Hematology, rabbits, *Eimeria stiedae*.

Introduction

The coccidiosis is parasitic disease with high spread in the rabbit farms (Oncel *et al.*, 2011; Qiao *et al.*, 2012; Laha *et al.*, 2015; Silva *et al.*, 2015). Two types of coccidiosis, intestinal and hepatic, are described in rabbits. Hepatic coccidiosis is caused by *Eimeria stiedae*. Affected livers are enlarged, and bile ducts are dilated. (Oncel *et al.*, 2011) and it is considered to be the most important disease faced by rabbit breeders, because of its high morbidity and mortality (Giorgi, 1968; Cardoso and Guimaraes Jr., 1993; Freitas *et al.*, 2011). Young rabbits are more susceptible to infection and the clinical condition generally observed is characterized by anorexia and diminished live and carcass weights, caused mainly by decreased food intake over the first four weeks (Freitas *et al.*, 2011).

There are a lot of studies concerning coccidiosis, caused by intestinal species: oocyst excretion (Papeschi *et al.*, 2013), immune response (Pakandl *et al.*, 2008), liver response (Al-Quraishy *et al.*, 2012), prevention (Drouet-Viard *et al.*, 1997), hematological parameters (Tambur *et al.*, 2001; Hana *et al.*, 2013), differential leucocyte count (Kulicic *et al.*, 2006). On the other hand, the data concerning some of the features of *E. stiedae* (hepatic species) infection are very poor: pathological signs (Al-Mathal, 2008; Abu-El-Ezz *et al.*, 2012), inflammatory response (Freitas *et al.*, 2011), treatment (Cam *et al.*, 2008).

To the best of our knowledge there is less information about blood profile in rabbits infected with *E. stiedae*. Therefore, the aim of this experiment was to supplement the available information concerning blood profile in rabbits with experimentally induced liver coccidiosis.

Materials and methods

Experimental animals and housing

The experimental procedure was approved by the Ethics Committee of the animals to the Bulgarian Agency for Food Safety. There were used 12 three-month-old, female New Zealand White rabbits keeping according to the requirements of Bulgarian legislation. During the experimental

period, the animals were individually housed in metal cages with a grid floor. Before infection, the rabbits were treated by anticoccidial drugs for 5 days and a week later were examined for presence of coccidian oocysts through routine flotation techniques. Water and pellet food were supplied *ad libitum*.

***Eimeria stiedae* oocyst isolation and inoculum preparation**

E. stiedae oocyst were obtained from liver of 2 naturally infected rabbits. The content of gallbladder and bile ducts was extracted by syringe and incubated with 2.5% potassium bichromate in petri dishes at 28 °C for 4 days. Sporulated oocyst were washed 4 times by distillate water and dialyzed against tap water for 24 hours. The inoculum was concentrated to 50 000 sporulated oocyst per 1 ml.

Design and duration of experiment

The rabbits were divided into experimental and control groups, each consisting of 6 animals. Each rabbit from experimental group was orally infected by 50 000 sporulated *E. stiedae* oocysts. Control rabbits were treated with saline by the same way.

Hematological tests

Blood samples were drawn with Na₂EDTA sterile tubes from *v. auricularis caudalis* from all rabbits before (0 hour) and 6, 24, 48 hours, and also 7, 14, 21, 28 days after infection with *E. stiedae*. The count of erythrocytes (Er), hemoglobin concentration (HGb), hematocrit (Hct), mean cell volume of erythrocytes (MCV), mean hemoglobin concentration in erythrocytes (MCH), mean concentration of corpuscular hemoglobin (MCHC), leucocytes (Leu), monocytes (Mo), granulocytes (Gran) and lymphocytes (Ly) were determined on the analyzer Exigo EOS Vet, Boule Medical AB, Sweden.

Statistical analysis

The data was performed using ANOVA (Statistics for Windows, Stat Soft.). All data were expressed as mean $\pm$ standard deviation (SD) and the differences were considered significant when $P < 0.05$.

Results

Red blood profile

The red blood profile is presented on Table 1. Er gradually decreased in both groups. Significant differences in Er count were established on 24th hour ($P < 0.05$) and 7th day ($P < 0.001$) in infected rabbits compared to initial level in the same group. For all experimental period there were no significant difference ($P > 0.05$) in Er values between experimental and control groups. After slight decreasing until day 7, the Er values started to increase and on day 14th was found significant difference ($P < 0.05$) in experimental group compared to 0th hour, but finally this parameter had a lower value compared initial level ($P < 0.001$). Although established decreasing of the hemoglobin concentration in both groups, the HGb values in experimental group were significantly higher ($P < 0.05$), compared the control group on 6th hour, 24th hour and 7th day. The results of Hct in

infected group followed the established decreasing in Er and HGb and we found significant differences ($P<0.05$) for this parameter in the period since 24th hour to the end of the experiment (28th day), except on 6th hour, where a significance of difference was higher ($P<0.01$). In the experimental group MCHC values on day 14 were significantly ($P<0.01$) lower compared to control group. On 28th day this parameter was significantly higher ($P<0.01$) compared to initial level. No significant changes ($P>0.05$) were established in MCV and MCH intra and inter groups.

In non-infected rabbits were established significant differences in Er on 24th hour ($P<0.05$) and 7th day ($P<0.01$) compared to hour 0. Significant changes in HGb were found on 24th ($P<0.01$), 48th hour ($P<0.05$) and 7th day ($P<0.001$) after infection compared to initial level. Significant changes were established in Hct on 6th ($P<0.05$), 24th ($P<0.01$) and 48th ($P<0.01$) hour compared to initial measurement. No significant difference ($P>0.05$) was established during the study concerning MCHC.

Table 1: Dynamics in parameters of red blood count in experimental group (*E. stiedae*) and control group rabbits (mean $\pm$ standart deviation)

	Er (10 ¹² /l)	HGb (g/l)	Hct (%)	MCV (fl)	MCH (pg)	MCHC (g/l)
Experimental group <i>E. stiedae</i> (n = 6)						
0 hour	5,75 $\pm$ 0,33	127,50 $\pm$ 3,27	35,77 $\pm$ 1,32	63,20 $\pm$ 1,86	22,47 $\pm$ 0,90	355,50 $\pm$ 6,66
6 hour	5,52 $\pm$ 0,35	120,83 $\pm$ 6,55 ^a	34,67 $\pm$ 1,78 ^{**}	63,38 $\pm$ 2,15	22,25 $\pm$ 0,88	354,33 $\pm$ 4,59
24 hour	5,30 $\pm$ 0,31 ^a	118,00 $\pm$ 5,87 ^{ab}	33,20 $\pm$ 1,56 ^b	62,67 $\pm$ 2,03	22,27 $\pm$ 0,71	355,67 $\pm$ 3,67
48 hour	5,05 $\pm$ 0,24	112,33 $\pm$ 4,93 ^c	31,60 $\pm$ 1,29 ^c	62,53 $\pm$ 2,08	22,25 $\pm$ 0,81	356,00 $\pm$ 4,77
7 day	5,00 $\pm$ 0,10 ^c	113,33 $\pm$ 3,67 ^c	31,55 $\pm$ 1,24 ^c	63,07 $\pm$ 2,18	22,68 $\pm$ 0,61	359,67 $\pm$ 5,54
14 day	5,20 $\pm$ 0,29 ^a	118,00 $\pm$ 5,06 ^b	33,63 $\pm$ 1,37 ^b	63,32 $\pm$ 2,44	22,48 $\pm$ 1,06	351,67 $\pm$ 5,09 ^{**}
21 day	4,94 $\pm$ 0,37	112,33 $\pm$ 8,07 ^c	30,98 $\pm$ 2,40 ^c	63,40 $\pm$ 2,27	23,00 $\pm$ 0,78	360,67 $\pm$ 9,16
28 day	4,81 $\pm$ 0,33 ^c	112,33 $\pm$ 8,07 ^c	30,38 $\pm$ 1,95 ^c	63,18 $\pm$ 1,76	23,15 $\pm$ 0,65	366,17 $\pm$ 5,00 ^b
Control group (n=6)						
0 hour	5,36 $\pm$ 0,33	117,83 $\pm$ 5,98	33,17 $\pm$ 0,98	61,18 $\pm$ 1,56	21,97 $\pm$ 0,60	354,50 $\pm$ 3,62
6 hour	5,14 $\pm$ 0,44	113,50 $\pm$ 6,32	31,17 $\pm$ 1,42 ^a	61,25 $\pm$ 1,67	21,68 $\pm$ 0,61	353,67 $\pm$ 5,54
24 hour	4,85 $\pm$ 0,43 ^a	105,33 $\pm$ 6,86 ^b	29,82 $\pm$ 2,34 ^b	61,47 $\pm$ 1,76	21,77 $\pm$ 0,72	354,00 $\pm$ 6,78
48 hour	4,99 $\pm$ 0,22	109,33 $\pm$ 5,79 ^a	30,68 $\pm$ 1,37 ^b	61,32 $\pm$ 1,70	21,87 $\pm$ 0,73	356,67 $\pm$ 6,83
7 day	4,69 $\pm$ 0,16 ^b	103,00 $\pm$ 3,85 ^c	30,12 $\pm$ 3,91	60,63 $\pm$ 1,64	22,07 $\pm$ 0,94	363,83 $\pm$ 9,70
14 day	5,15 $\pm$ 0,51	112,17 $\pm$ 8,47	31,12 $\pm$ 2,60	60,50 $\pm$ 2,00	21,92 $\pm$ 0,79	362,00 $\pm$ 8,10
21 day	5,24 $\pm$ 0,36	112,67 $\pm$ 6,53	31,35 $\pm$ 1,94	59,85 $\pm$ 1,87	21,57 $\pm$ 1,13	359,83 $\pm$ 9,85
28 day	5,21 $\pm$ 0,37	110,33 $\pm$ 10,09	30,92 $\pm$ 2,56	59,42 $\pm$ 2,58	21,30 $\pm$ 1,26	357,33 $\pm$ 6,80

* $P<0.05$, ** $P<0.01$, significant difference between groups; ^a $P<0.05$, ^b $P<0.01$, ^c $P<0.001$, significant difference vs 0 hour.

White blood profile

The results concerning white blood profile are presented in Table 2. During the study we established significant increasing ($P<0.05$) in Leu, Gran, Mo and Ly since 14th to 21st day between groups. In the experimental group we found significant increasing in Leu ($P<0.05$), Gran ($P<0.05$) and Mo ($P<0.01$) on 14th day compared to initial measurement. On day 21 there is a significant increasing in Gran and Mo count only ($P<0.05$) in the experimental group.

There is found a significant decreasing in Ly level at 6th hour ($P<0.01$) and 28th day ($P<0.05$) compared to initial level in the experimental group. In the control group we established slight significant increasing in Leu on 14th and 21st day ($P<0.05$) compared to hour 0.

Table 2: Dynamics in parameters of white blood count in experimental group (*E. stiedae*) and control group rabbits (mean $\pm$ standart deviation)

	Leu 10⁹/l	Gran 10⁹/l	Mono 10⁹/l	Lymph 10⁹/l
Experimental group <i>E. stiedae</i> (n = 6)				
0 hour	10,75 $\pm$ 1,33	4,82 $\pm$ 1,14	0,88 $\pm$ 0,16	5,08 $\pm$ 0,66
6 hour	10,38 $\pm$ 1,82	5,87 $\pm$ 1,44	0,83 $\pm$ 0,23	3,68 $\pm$ 0,58 ^b
24 hour	9,93 $\pm$ 1,20	4,67 $\pm$ 0,90	0,85 $\pm$ 0,10	4,42 $\pm$ 0,52
48 hour	10,08 $\pm$ 1,14	4,22 $\pm$ 0,88	0,83 $\pm$ 0,12	5,03 $\pm$ 0,97
7 day	9,57 $\pm$ 1,31	3,87 $\pm$ 0,96	0,72 $\pm$ 0,15	4,98 $\pm$ 0,69
14 day	16,10 $\pm$ 5,28 ^a	7,22 $\pm$ 2,33 ^a	1,38 $\pm$ 0,35 ^b	7,50 $\pm$ 2,79 ^{**}
21 day	13,33 $\pm$ 3,13 ^{**}	6,93 $\pm$ 1,85 ^a	1,35 $\pm$ 0,45 ^{**a}	5,05 $\pm$ 1,40 ^{**}
28 day	10,92 $\pm$ 1,78	5,73 $\pm$ 0,96	1,08 $\pm$ 0,18 [*]	4,10 $\pm$ 0,80 ^a
Control group (n = 6)				
0 hour	9,05 $\pm$ 1,05	3,80 $\pm$ 0,58	0,72 $\pm$ 0,16	4,53 $\pm$ 0,56
6 hour	8,85 $\pm$ 0,91	4,43 $\pm$ 1,15	0,78 $\pm$ 0,15	3,63 $\pm$ 0,92
24 hour	8,82 $\pm$ 1,03	4,17 $\pm$ 0,65	0,83 $\pm$ 0,08	3,82 $\pm$ 0,58
48 hour	9,33 $\pm$ 1,04	4,22 $\pm$ 0,96	0,85 $\pm$ 0,14	4,27 $\pm$ 1,16
7 day	9,73 $\pm$ 0,80	4,00 $\pm$ 0,60	0,73 $\pm$ 0,25	5,00 $\pm$ 0,65
14 day	9,43 $\pm$ 0,58 ^a	4,33 $\pm$ 0,98	0,75 $\pm$ 0,21	4,35 $\pm$ 0,88
21 day	9,47 $\pm$ 0,97 ^a	5,18 $\pm$ 1,47	0,65 $\pm$ 0,30	3,63 $\pm$ 0,83
28 day	9,93 $\pm$ 0,59	4,73 $\pm$ 1,03	0,75 $\pm$ 0,10	4,45 $\pm$ 1,11

* $P < 0.05$, ** $P < 0.01$, significant difference between groups; ^a $P < 0.05$, ^b $P < 0.01$, significant difference vs 0 hour.

Discussion

A lot of studies concerning red blood count after experimentally provoked infection in animals, reported anemia during the study (Mohamed, 2009; Praveena et al., 2010; Petrov et al., 2011; Hana et al., 2011; Petrov & Mircheva, 2013), independantly from the used agent (*P. multocida*, *E. coli*, *E. magna*, *S. aureus*, respectively). Our results, confirmed the study by Freitas et al. (2011), who described anemia, which has due to the decreased Er, HGb and Hct, after invasion with sporulated oocysts of *E. stiedae*. In this direction are also the results of Hana et al. (2013), which reported anemia after *E. magna* infection in rabbits. The authors presumably proposed that the reason for its occurrence is the damage of the intestinal mucosal epithelium and blood vessels by the coccidia. Our results partially support Cam et al. (2008), regarding HGb, Hct and MCV, who reported decreasing of these parameters, where in our research we found out only a slight decreasing in MCV values. This difference may be due to the different doses of *E. stiedae* oocysts and the severity of infection. Along with that, our research showed increasing of MCHC in diseased animals, which is similarly with the results by Adamu et al. (2013) in chickens. The registered increasing of this parameter may be related to the increased relative density of the blood, caused by the diarrhea as a consequence of the first oocyst excretion established in our study. Hashemnia et al. (2014) have recently reported increasing of HGb and MCV in goats, which is in contrast with our results. We proposed that the different invasive agent and different animal species, used for the comparison with our results, could be the reason for the established changes between our study and aforementioned results.

Our study confirmed the available information concerning the anemia in the chronic inflammatory diseases (Harvey, 2008) and the inflammatory response during *E. stiedae* infection (Freitas et al., 2011). We assumed that the reduction of Er, HGb and Hct could be a result of liver damage and the subsequent inflammation in the infected animals, as well as the prolonged blood collection by the healthy rabbits.

The leucocytes are a part of the defense mechanisms against foreign agents such as parasites and *E. stiedae* induce inflammatory reaction in the infected rabbits, leading to transport of leucocytes to the inflammation areas. Except in rabbits, leucocytosis was also reported in chickens, dogs, sheeps and goats, during *Eimeria* species infection (Turk, 1986; Adamu et al., 2013; Kaymaz et al., 1999; Sahinduran et al., 2006; Hashemnia et al., 2014). Our data and the data by Cam et al. (2008) and Freitas et al. (2011), confirmed the claim that the infectious agent *E. stiedae* induced leucocytosis in rabbits. Although, this coccidia induced increasing in the number of the monocytes in the peripheral blood in the first hours after infection (Slater et al., 1969; Owen, 1970), our results did not show a change in their number in the early hours of the experiment. Cam et al. (2008) and Freitas et al. (2011) reported increased monocytes number in the end of the experimentally induced *E. stiedae* infection. The present study partially supports the data mentioned above and described higher values of the monocytes throughout the second half (last two weeks) of the tested period. We proposed that the manifestation of this experimental monocytosis at different times, could be due to the different infectious doses of *E. stiedae*, used in our research and the aforementioned studies.

The eosinophils are a part of the granulocytes leucocytes and their increasing serves as an indicator of the parasitic diseases. Concomitantly, *E. stiedae* is a protozoan intracellular parasite and do not induce eosinophilia. The activity of granulocyte macrophage colony-stimulating factor induces the formation of granulocytes (including eosinophils) from the bone marrow stem cells (Al-Tae and Al-Zubaidi, 2017) and the established very high levels of granulocytes during our experimental period supports this claim.

The immunity against intracellular microorganisms is only cell mediated immunity type (Al-Tae and Al-Zubaidi, 2017) and the lymphocytes have a primary function for this response. Also, the local immune response mediated by the gut associated lymphoid tissue plays more important role in the immunity to coccidiosis than the systemic response (Pakandl, 2009). Furthermore, there are researches (Smetana, 1933a; Horton, 1967; Fitzgerald, 1970; Pellerdy and Durr, 1970), established sporozoites of *E. stiedae* at the lymphoid cells in the mesenteric lymph nodes (MLN) (Pakandl, 2009). Therefore, we proposed that the registered in our study decreasing in the lymphocytes and the subsequent lymphocytosis could be due to the migration of the parasites through MLN and the caused cell-mediated immune response against *E. stiedae*. The increase in the total number of white blood cells may be due to increased lymphocytes, associated with the immune response to the infectious agent. The received high values of the total and differential white blood count confirmed that *E. stiedae* cause inflammatory reaction in the receptive animals.

Conclusion

The present study concluded that *E. stiedae* infection in rabbits cause significant changes in the parameters of the red and white blood profile. We established decrease of erythrocytes, hemoglobin, hematocrit, and also increase of mean concentration of corpuscular hemoglobin, leucocytes, granulocytes, monocytes and lymphocytes. The results of the conducted study showed that the blood profile could be useful for diagnosing and prevention of the liver coccidiosis in rabbits.

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