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Efficacy of Darbepoetin alfa in anemic dogs with Chronic Kidney Disease – a review of 21 cases

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Abstract

Anemia due to Chronic Kidney Disease (CKD) represents a major portion of hemodynamic imbalance in dogs. Although the pathogenesis of the anemia in CKD is multifactorial, decreased production of erythropoietin by the diseased kidneys has been proven and the severity of anemia correlates positively with serum creatinine concentrations in affected dogs.

Therapeutic whole and Packed Red Blood Cell transfusion has always been a main stay in practice. However, the unavailability of appropriate dog donors, blood typing modalities and occurrence of post transfusion reactions are the common hurdles encountered. Alternatively, Darbepoetin alfa, a hyperglycosylated synthetic recombinant erythropoietin which is commonly used in human patients with CKD induced anemia is used in recent canine practice. Unlike human transfusion medicine, not much of study has been documented in dogs in India. However anecdotally, darbepoetin is perceived to less likely form antibodies compared to erythropoietin. A study comprising of 21 dogs referred to Madras Veterinary College Teaching Hospital (MVCTH) with CKD (stage II, III & IV were 7, 9 & 5 respectively) of multifactorial etiology during the period of January to December 2017 was done. Injectable Darbepoetin was administered @0.5µg/kg subcutaneously once in a week for three weeks along with supplementation of Iron to achieve a medium hematocrit of 30%. Efficacy of Darbepoetin was evaluated by measuring pre and post therapeutic clinico pathological studies. Darbepoetin proved effective in increasing PCV, anemic crisis potentially in 66.7% of dogs. Hypertension, vomiting, melena, inappetance were common findings in affected dogs and coexistence of normocytic, normochromic progressive anemia which responds to Darbepoetin alfa therapy. Though expensive than Erythropoietin, Darbepoetin @0.5µg/kg s/c proved safe and effective in improving packed cell volume in CKD dogs as an alternative to packed RBC or whole blood transfusion. Further immunological, toxicological and clinical studies on Darbepoetin therapy is warranted in a large population in dogs.

Keywords: Ckd; Azotemia; Anemia; Darbepoetin

Introduction

Canine kidney disease is the most common cause of morbidity and mortality in dogs. In Chronic Kidney Disease (CKD), irreversible and progressive damage to the kidneys results in excretory, fluid, acid-base and electrolyte abnormalities leading to accumulation of metabolic waste substances like BUN and Creatinine (Grauer, 2017). Kidney is the primary source of erythropoietin, which is responsible for the production of RBC from bone marrow. But in CKD dogs, gradual reduction in functional mass may leads to deficiency of erythropoietin ends up with anemia. Darbepoetin alfa, a hyperglycosylated synthetic recombinant erythropoietin analog is commonly used in human patients with CKD induced anemia (Polzin, 2013). Efficacy and role of Darbepoetin was not much evaluated in dogs in India, hence present study was conducted to assess the severity of anemia in CKD dogs and to assess the efficacy of Darbepoetin in anaemic dogs with CKD.

Chronic kidney disease (CKD) is a metabolic disorder of companion animals, estimated to occur in 0.4–1.5% of dogs and represented in a higher percentage of older dogs and those evaluated at tertiary care facilities.(O'Neil,2013).

A progressive, normocytic, normochromic hypo proliferative anemia develops as a feature of CKD, and although there are no published data on the prevalence of anemia in dogs with CKD, it is expected to occur in most dogs that progress to end-stage disease. (Cowgill, 2013 and Bartges, 2012)

In addition to contributing to lethargy, anorexia, and weakness, severe anemia may exacerbate progression of CKD because of decreased oxygen delivery to the residual kidney. (Chakrabarti, 2012)

Egrie *et al*, 2003 reported that erythropoiesis-stimulating agents (ESA) are administered to some dogs with anemia secondary to CKD. Epoetin alfa (epoetin) was the first ESA used in human and veterinary medicine, but it has largely been replaced by darbepoetin alfa (darbepoetin) due to a 3-fold longer half-life, allowing for less frequent dosing.

Materials and Methods

Twenty one dogs of different breeds and age groups were presented to Madras Veterinary College Teaching Hospital, Chennai with CKD (IRIS, 2017) (stage II , III & IV were 7, 9 & 5 respectively) of multifactorial etiology during the period of

January 2017 to December 2017 were studied. Darbepoetin was administered @0.5µg/kg subcutaneously once in a week for four weeks along with supplementation of Iron injection to achieve a medium hematocrit of 30%. Efficacy of Darbepoetin was evaluated by clinical and hematological studies.

Result and Discussion

Pre therapeutic hemoglobin (g/dl), PCV (%) and Total erythrocytic counts (m/cmm) were 10.7, 32.4 & 4.1 (Stage II), 9.1, 24.1 & 3.42 (Stage III) and 7.9, 20.3 & 3.21 (Stage IV) respectively. Post therapeutic hematological parameters were depicted in table 3. Darbepoetin proved effective in increasing PCV, anemic crisis potentially in 66.7% of dogs. Hypertension, vomiting, melena, inappetance were common findings in affected dogs and coexistence of normocytic, normochromic progressive anemia which responds to Darbepoetin alfa therapy. Though expensive than Erythropoietin, Darbepoetin @0.5µg/kg s/c proved safe and effective in improving packed cell volume in CKD dogs as an alternative to packed RBC or whole blood transfusion.

Five dogs under study showed no much response to the administered Darbepoetin and underwent Packed RBC transfusions transiently. Four of these dogs died on the following months of treatment for severely increased azotemia (stage IV).

Table 1: Staging of Chronic Kidney Disease (CKD) dogs based on IRIS, 2017 classification

	Stage of CKD	Creatinine level	No. of cases included
1	I	1.5	None
2	II	1.5-2.0	7
3	III	2.1-5.0	9
4	IV	>5.0	5

Table 2: Hematological parameters in different stages of CKD dogs

	Hb	PCV	RBC	WBC	Platelet count	N	L	M	Blood picture
Stage II	10.9	29.06	4.734	24220	4.126	81.2	13.2	4.6	Hypochromasia
Stage III	10.05	26.23	4.134	6907	2.344	75	19.07	4.78	Hypochromasia
Stage IV	7.689	20.36	3.004	10022	2.751	77	17.75	4.37	Anisocytosis, polychromasia

Table 3: Pre and post therapeutic hematological parameters in CKD dogs

	Hb	PCV	RBC	WBC	Platelet count	N	L	M	Blood picture
Stage II	10.9	28.06	4.7	24220	4.13	81.2	13.2	4.6	Hypochromasia
after	11.8	31.92	5.1	10989	2.97	74.67	20.4	4.2	Hypochromasia
Stage III	10.05	26.23	4.1	6907	2.34	75	19.0	4.7	Hypochromasia
After	10.53	30.56	5.0	10471	2.42	76	17	5.1	Hypochromasia
Stage IV	7.68	20.36	3.0	10022	2.75	77	17.7	4.3	Anisocytosis, polychromasia
after	All cases in this group were died within 2-3 weeks of presentation								

Summary & conclusion

In conclusion, Darbepoetin proved effective in increasing PCV, anemic crisis potentially in 66.7% of dogs @0.5 to 0.8 µg/kg s/c weekly till target PCV achieved. Though expensive than erythropoietin, Darbepoetin @0.5µg/kg s/c proved safe and effective in improving packed cell volume in CKD dogs as an alternative to packed RBC or whole blood transfusion. Further immunological, toxicological and clinical studies on darbepoetin therapy are warranted in a large population.

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