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Study on Effect of Filgrastim in Severe Leukopenia Condition in Dogs

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A B S T R A C T

Filgrastim is a recombinant Methionyl Human Granulocyte- Stimulating Factor (r-metHuGCSF) analog used to stimulate the proliferation and differentiation of granulocytes in humans. Young pups and kittens suffer from severe leukopenia and neutropenia condition (etiology may be viral or bacterial or parasitic). Neutrophils being first line of defense in immunity system and decreased count may lead to increased mortality. In the present investigation 3 dogs with severe leukopenia and neutropenia condition when treated dogs with Filgrastim @ 10 µg/ kg b.wt. s.c daily for three days along with other supportive treatment, was found to be effective in correcting the hematological parameters within 48 hours of last dose of treatment and all those showed fast recovery also.

Introduction

Filgrastim (Grastim®) is a recombinant Methionyl Human Granulocyte Colony- Stimulating Factor (r-metHuG-CSF) analog used to stimulate the proliferation and differentiation of granulocytes in humans undergoing chemotherapy with granulocyte values below 0.5 G/I likely to be threatened by infections, including sepsis possibly with a fatal outcome (Novotny *et al.*, 1995). Filgrastim is a non-glycosylated, 175 amino acid containing protein, which is produced recombinantly by *E. coli*. Filgrastim has a molecular weight of 18.8 kDa. It regulates the production and release of functional neutrophils from bone marrow within 24 hours of administration. Filgrastim results in increase in peripheral blood neutrophil counts with minor increases in monocytes (Areshkumar *et al.*, 2017).

Neutropenia frequently occurs in dogs mainly by Canine Parvoviral infection along with other several different causes (Macartney *et al.*, 1984), also majorily by Canine distemper Virus, Bacterial infections like *E.coli* and *Colistridium* spp and also Parasitic infections etc. Out of these, canine parvovirus remains the most significant viral cause

of hemorrhagic gastroenteritis in dogs less than 6 months of age (Appel *et al.,* 1979). Canine parvovirus has a predilection for rapidly dividing cells, making the granulocyte precursor pool in the bone marrow a prime target for destruction in young pups. In addition, loss of neutrophils may occur through the damaged gastrointestinal tract (Fulton *et al.,* 1991). Neutrophils are most important cells required for immune system to combat with the bacterial infection. So prolonged neutropenia greatly increases the risk of death, due to sepsis. Hence strategies are required to shorten the duration of neutropenia in dogs.

The use of granulocyte- colony stimulating factor, a cytokine and growth factor that potently stimulates neutrophil production and release from the bone marrow, has been advocated for treatment of parvovirus- induced neutropenia (Kraft and Kuffer, 1995). Haematopoietic growth factors that stimulate leukocyte generation and or differentiation are important in the response to infection (Rewerts and Henry, 1998). The primary clinical use of G-CSF in humans is mainly for management of chemotherapy-induced neutropenia (Czygier *et al.,* 2007). In veterinary medicine, rcG- CSF has also been evaluated for use in management of chemotherapy-induced neutropenia (Ogilvie *et al.,* 1992). Therefore, a case study was conducted on 3 dogs of severe leukopenia were treated with filgrastim correcting haematological abnormalities and stimulated more rapid recovery of leucocytes and neutrophil counts

Materials and Methods

In our present study three dogs which were suffering from severe leukopenia were taken. Mostly having clinical signs of hemorrhagic gastroenteritis with different grades of dehydration. The blood sample (2ml) was collected in a vial containing EDTA and subjected to haematological examination (haemoglobin, packed cell volume, total and differential leucocyte count, thrombocyte count) with the help of automatic haematology analyser (H 560 Erba Manheim) those values were given in Table 2. Affected dogs were treated with Inj. Filgrastim @ 10 µg / kg b.wt. subcutaneously once daily (Morris and Dobson, 2001).

For three days along with supportive therapy (intravenous fluid, antibiotics and antiemetics) was given in Table 1. The blood samples were collected again on day 3 post treatment and data was analysed and interpreted in Table 3.

Results and Discussion

Canine parvo viruses, Canine Distemper, Feline pan leukopenia, other Bacterial, Parasitic infections like Tick fever cases in dogs are life-threatening problem where severe leukopenia noticed. Although the dogs which were not vaccinated properly suffered the most, but occurrence of the disease was also noticed in vaccinated dogs and the leukocytes count was very low. Greene and Decaro (2012) reported that those pups dying from Parvovirus disease generally have TLC equal to or less than 1030 cells/µl and have persistent lymphocytopenia, monocytopenia and eosinopenia within the first 3 days of hospitalization. Haematological parameters revealed marked leukopenia with neutropenia in all the cases at day of presentation. WBC count was found to be 1.4 ± 0.17 thousand per mm^3 and neutrophil count was found to be 1.96 ± 0.17 thousand per $mm^{3,}$ Remaining haematological findings are given in table 2. To overcome this critical situation in the present study Inj. Filgrastim at the dose rate of 10 µg/kg body weight by S/C route was administered daily for about three days. After 72 hours of the injection, the WBC count found to be elevated significantly by 8.38 ± 0.57 thousand per mm^3. There was significant difference in neutrophil count by 5.07 ± 0.31 thousand per mm^3 and lymphocyte count by 1.63 ± 0.19 thousand per mm^3 of day 1 and day 3 post treatment samples because filgrastim mainly acts on bone marrow and it increases production of leucocytes.

Table.1 Supportive therapy given to the animals (depending on clinical condition)

Drug	Drug Dose (per Kg B.wt)
Inj. Dextrose 5%	10-20ml depending on grade of dehydration
Inj. Lactate ringer solution	15-30ml depending on grade of dehydration
Inj. Metronidazole	25mg
Inj. Astymin ® (cocktail of amino acids)	1ml
Inj. Ondansetron	0.1mg
Inj. Pantoprazole	1mg
Inj. Gentamycin	6mg

Table.2 Hematological pictures of dogs suffering from severe leukopenia (n=3)

Parameter	Day 1			Day 3 Post Treatment		
Patient	**Dog**			**Dog**		
	1	2	3	1	2	3
Hemoglobin (g/dL)	10.4	12.1	11.2	10.2	11.8	11
RBC (million/mm^3)	4.4	5.86	5.4	4.3	5.39	5.32
WBC (cells/µL)	**1100**	**1700**	**1400**	**8200**	**9450**	**7500**
Neutrophils (10 ^{3}cells/mm^3)	**1.7**	**2.4**	**1.8**	**6.5**	**7.6**	**7.0**
Lymphocytes (10 ^{3}cells/mm^3)	2.3	3.0	2.9	3.9	4.5	4.7
Platelets (lakhs/µl)	3.7	4.5	4.2	3.9	4.2	4.4
PCV (%)	39	50	45	35	45	47

Table.3 Comparison of different hematological parameters of blood samples of Day1 and Day3 Post treatment (n=3)

Parameter	Day1 before treatment	Day 3 Post treatment
Hemoglobin (g/dL)	11.23±0.49	11±0.46
RBC (million/mm^3)	5.22±0.39	5.0±0.35
WBC (cells/µL)	1.4±0.17^a	8.38±0.57^b
Neutrophils (10^3 cells/mm^3)	1.96±0.17^c	7.03±0.31^d
Lymphocytes (10^3 cells/mm^3)	2.73±0.17^e	4.36±0.19^f
Platelets (lakhs/µl)	4.13±0.19	4.23±0.30
PCV (%)	44.66±3.18	42.33±3.71

*Mean (±SE) bearing different superscripts (a, b) differ significantly (p< 0.05) on Day 1 and day 3 post treatment
*Mean (±SE) bearing different superscripts (c, d) differ significantly (p< 0.05) before and after treatment
*Mean (±SE) bearing different superscripts (e, f) differ significantly (p< 0.05) before and after treatment
There is no significant difference between Hb, PCV, RBC and Platelets count on Day1 and Day3 post treatment

Although there was no significant increase in hemoglobin, RBC, PCV and Platelet count as shown in Table 2 as there is no effect of filgrastim on erythropoiesis or thrombocyte production. Rewerts *et al.*, 1998 and Mischke *et al.*, 2001 did not find any improvement in neutrophil counts or duration of

hospitalization in treated animals when compared to untreated animals in cases. However Ogilvie *et al.*, (1992); Kraft and Kuffer (1995); Duffy *et al.*, (2009); Areshkumar *et al.*, (2017) and Sunil punia *et al.*, (2021) found significantly increased neutrophil counts compared to control dogs suffering from neutropenia. So, from the present study we concluded that administration of Filgrastim may improve the survival rate if it is administered at the early stage of the disease along with other supportive therapy as uneventful recovery was received in all the treated cases.

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