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Comparison of Oral Prednisolone, Budesonide and Probiotics in the Treatment of Canine Inflammatory Bowel Disease

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ABSTRACT

Background: Inflammatory bowel disease (IBD) is the common cause of chronic gastrointestinal signs in dogs. The treatment possesses numerous difficulties due to the idiopathic nature of the disease. Conventional steroid therapy usually produces side effects on long term usage. Thus, there is a need for alternative therapies. When compared to human medicine, there is no published data on the use of budesonide and probiotic in the treatment of canine IBD in India. The present study was proposed to compare oral prednisolone, budesonide and probiotics in the management of canine inflammatory bowel disease.

Methods: Thirty dogs with idiopathic IBD were selected and randomly grouped. They were subjected to therapy involving prednisolone, budesonide or probiotics. Clinical assessment was performed by calculation of the post treatment Clinical Inflammatory Bowel Disease Activity Index (CIBDAI) score, faecal score and endoscopy. Biochemical analysis of alkaline phosphatase and alanine transaminase were done to record side effects of steroid administration.

Result: It was observed from the present study that both prednisolone and budesonide are equally effective in the management of IBD in dogs. Probiotics were found to be less effective when compared to prednisolone and budesonide in the treatment of IBD.

Key words: Budesonide, Canine, CIBDAI, Endoscopic score, IBD, Prednisolone, Probiotics.

INTRODUCTION

The treatment for canine inflammatory bowel disease IBD is aimed at reducing inflammation and in many instances, suppressing an overactive immune system. Practical drug treatment recommendations for IBD are determined by disease severity and clinical course (*e.g.,* presence of mild IBD versus PLE), the involved segments of the alimentary tract, size of the patient impacting drug costs and the potential risks or side-effects associated with use of some medications. Most veterinarians prefer a sequential approach to nutritional and drug therapy for IBD. The optimal drug or drug combination as well as duration of therapy for induction and maintenance of remission of clinical signs have not been determined for most protocols (Arslan, 2017).

Often corticosteroids (*e.g.,* prednisone, prednisolone) are used as first-line therapy for canine. However, these therapies are always observed to have side effects during long term administration. Budesonide, a steroid which is being used in human IBD have proved to have fewer side effects when compared to prednisolone. In recent past, human IBD patients have gradually switched over for alternative therapies. Studies in human and animal medicine suggest that the intestinal microbiota plays a crucial role in the pathogenesis of IBD and modulation of intestinal microbiota may be beneficial in the treatment of mucosal inflammation (Rioux *et al.,* 2005 and Suchodolski *et al.,* 2012). In human medicine, studies with VSL#3 a high-dose, multi-strain probiotic product containing viable lyophilized bacteria consisting of 4 strains of *Lactobacillus* (*L. casei*, *L. plantarum*. *L.acidophilus* and *L. delbrueckii* subsp. *bulgaricus*), 3 strains of *Bifidobacterium* (*B. longum*, *B. breve* and *B. infantis*) and 1 strain of *Streptococcus sulivarius* subsp *thermophilus* have demonstrated the beneficial effects in the prevention and treatment of pouchitis and in maintaining remission of mild to moderate ulcerative colitis, so that probiotics could provide safe alternatives to conventional treatments (Bibiloni *et al.,* 2005 and Turner *et al.,* 2012). Similarly, Rossi *et al.* (2014) observed a protective effect of the probiotic mixture formulated with VSL#3 in dogs with IBD, with a significant decrease in clinical and histological scores and a decrease in CD3+ T-cell infiltration when compared with combination drug therapy group (prednisone and metronidazole). Protection was associated with an enhancement of regulatory Tcell markers (FoxP3+ and TGF-b+) and normalization of dysbiosis, specifically observed in

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the probiotic-treated group. These results suggest that probiotics (with elimination diet) can be used alone (Rossi *et al.,* 2014) or as adjuvant with standard therapy (steroid therapy and elimination diet) (Bibiloni *et al.,* 2005 and Turner *et al.,* 2012) in the management of IBD.

Budesonide therapy and non-traditional therapies (prebiotic/probiotic therapy) for canine IBD are in their infancy when compared to human IBD. Further, there is no discrimination between drugs prescribed for either induction or maintenance of remission (Jergens *et al.,* 2010).

With this background, the present study was planned and conducted to compare oral prednisolone, budesonide and probiotics in the management of canine inflammatory bowel disease.

MATERIALS AND METHODS

Selection of cases

The study was conducted at the Small Animal Medicine Outpatient Unit of Madras Veterinary College, TANUVAS, Chennai from 2014 to 2016. The dogs were included based on the previously published criteria by WSAVA (Washabau *et al.,* 2010) for the diagnosis of idiopathic IBD: persistent (>3 weeks duration) or recurrent gastrointestinal signs, inadequate response to dietary and antibiotic therapies, thorough diagnostic evaluation with exclusion of other causes of gastroenteritis and histopathological evidence of mucosal inflammation.

Routine haematology, serum biochemistry, faecal analysis for parasites and histopathologic review of endoscopic mucosal biopsy specimens were done to rule out other possible causes of chronic gastrointestinal signs. Thirty confirmed cases of idiopathic IBD with diffuse lymphoplasmacytic infiltration based on endoscopic histopathology were selected for the study.

Treatment protocols

The selected dogs were equally divided and randomly subjected to treatment protocols as per Dye *et al*. (2013) (Prednisolone and Budesonide) and Rossi *et al.* (2014) (Probiotics). The treatment protocols were prescribed for 6 weeks along with elimination diet consisting of potato/ lamb meat and rice.

Group A- Prednisolone orally at a dosage of 1 mg/kg q24 h for 3 weeks then 0.5 mg/kg q24 h for 3 weeks.

Group B- Budesonide in capsule form orally with dosage based on body weight as follows: 3-7 kg: 1 mg budesonide q24 h; 7.1-15 kg: 2 mg budesonide q24 h; 15.1-30 kg: 3 mg budesonide q24 h; >30 kg: 5 mg budesonide q24 h.

3. Group C- Probiotic (GUTWELL ®powder, Venkys) orally based on body weight. Small breeds-2 g twice a day, Medium breeds - 3 g twice a day and Large and gaint breeds - 5 g twice a day. Each gram provided 800 million CFU of probiotics (*Saccharomyces cervisiae, S. boulardii, Lactobacillus Complex* (*L. acidophilus, L. casie, L. rahmnosus*) and 20 mg of Prebiotics (Fructo-Oliga-Saccharides). It is fortified with enzyme complex containing protease, lipase, amylase, beta glucanase, cellulase, hemicellulase and pectinase.

Additionally, the dogs were given metronidazole at the dose of 15 mg/kg q12 h orally for six weeks. Supplementation of cobalamin in dogs with subnormal serum cobalamin level (<200 ng/L) as done at the dose of 500-1000 µg subcutaneously once weekly for six weeks.

Treatment evaluation

Dogs were re-evaluated at 6 weeks after initiation of drug therapy. Clinical assessment was performed by calculation of the pre and post treatment CIBDAI score, faecal score and endoscopy findings as per the performa of Jergens *et al*. (2003), Westermarck *et al.* (2005) and Washabau *et al*. (2010) respectively. Biochemical analysis of alkaline phosphatase (ALP) and alanine transaminase (ALT) were done to record side effects of steroid administration.

Statistical analysis

Qualitative data are presented in the form of percentages. Arithmetic means and standard error were used to describe quantitative data. Student's t distribution for independent samples was used to analyze the differences between pre and post treatment within the group. One way ANOVA was used to analyse the difference values of post and pre treatment CIBDAI values of different groups to know the treatment outcome. The data obtained in the study were subjected to statistical analysis using SPSS 23.0 and discussed.

RESULTS AND DISCUSSION

The pre treatment and post treatment values of various parameters under study for the three therapeutic protocols are summarized in Table 1-6.

In the present study, prednisolone treated IBD dogs (Group A) showed more than 50 per cent reduction in the CIBDAI scoring post treatment (Table 1). The faecal

Table 1: Mean±S.E values of CIBDAI score- pre and post treatment.

Parameter	Days	Group A (n=10)	Group B (n=10)	Group C (n=10)
CIBDAI	Pre	6.5±0.45	9.40±0.72	7.20±0.47
	Post	2.70±0.44	4.30±0.42	4.90±0.35
	t value	7.943**	11.769**	7.662**

**- Statistically highly significant (P<0.01).

*- Statistically significant (P<0.05).

NS-Statistically non significant (P>0.05).

consistency of score 4 to 5 at pretreatment improved to score of 3 and 4 (Table 2) (Fig 1). Post treatment endoscopic examination in these dogs identified a significant decrease in the intensity of the intestinal lesion such as hyperemia, friability and haemorrhage (Table 3) (Fig 2). Highly significant reduction in the post treatment endoscopic score was also observed (Table 4). This clinical, faecal and endoscopic lesion improvement with prednisolone after six weeks in the present study was comparable with the findings of Jergens *et al*. (2010) and Dye *et al*. (2013). Similarly, Luckschander *et al*. (2006) also reported that a 10-week trial of prednisolone reduced clinical (CIBDAI) scores and endoscopic scores of IBD dogs post treatment.

Marked clinical improvement in the form of a more than 50 per cent reduction in the CIBDAI scoring after six weeks was observed in the IBD dogs treated with budesonide. (Group B) (Table 1). The faecal consistency of 4.5 to 5 at pretreatment improved to 3 and 4 (Table 2) (Fig 1). In post treatment endoscopy there was marked decrease in the number of cases presenting the predominant intestinal lesions (Table 3) (Fig 3). Highly significant reduction in the post treatment endoscopic score was observed (Table 4).Our results were comparable to Peitra *et al*. (2013) who observed clinical, faecal and endoscopic lesion improvement after 20 days of budesonide administration to IBD dogs and to Dye *et al*. (2013) who recorded clinical improvement after 6-week treatment trial. However, in a recent study, Rychlik *et al*. (2016) stated that the drug failed to alleviate clinical symptoms of the disease and decrease the CIBDAI scores and the endoscopic scores. This contradiction may be due to the location of disease. In humans, budesonide is mainly used in the case of Crohn's disease which involves the inflammation of small intestine (Campieri *et al.,* 1997). The reason for improvement noticed in the budesonide treated IBD dogs of present study might be due to the presence of diffuse IBD which was evident on histopathology.

Table 2: Faecal scoring- pre and post treatment.

Faecal scoring	Group A (n=10) (Per cent)		Group B (n=10) (Per cent)		Group C (n=10) (Per cent)	
	Pre	Post	Pre	Post	Pre	Post
3 (beginning to lose form, leaving a definite mark when picked up)		60	-	30	-	-
4 (soft faeces)	20	40	-	70	-	20-
4.5 (very soft faeces)	70	-	50	-	40	40
5 (diarrhoea)	10	-	50	-	60	40

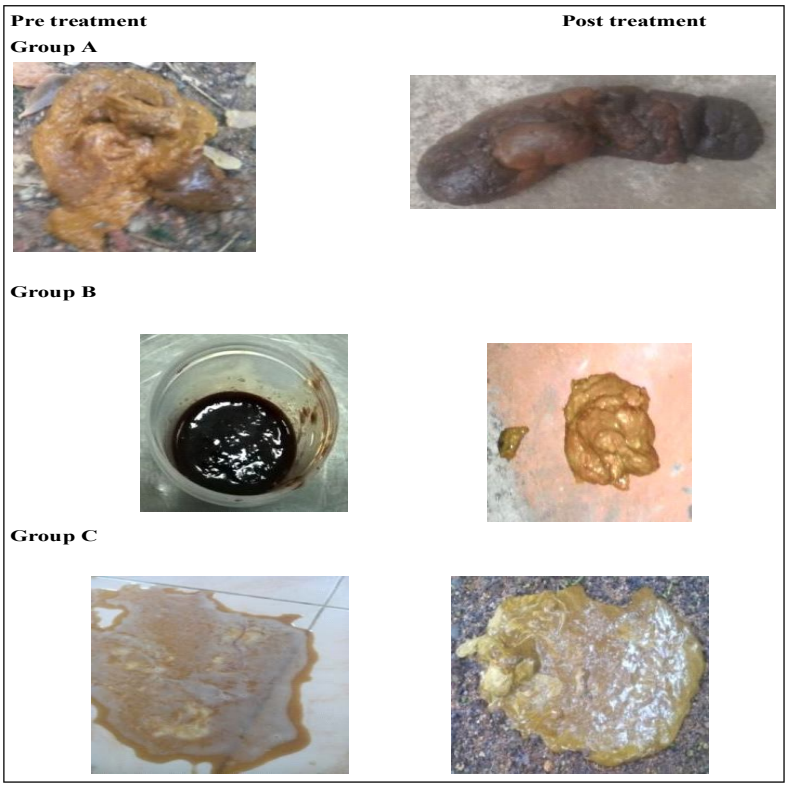


Fig 1: Faecal changes - pre and post treatment.

Table 3: Endoscopic findings in Stomach, Duodenum and colon- pre and post treatment.

Parameters	Severity of lesion	Group A (n=10)						Group B (n=10)						Group C (n=10)					
		Stomach		Duodenum		Colon		Stomach		Duodenum		Colon		Stomach		Duodenum		Colon	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Hyperaemia (%)	Mild	60	40	50	60	20	30	20	30	20	20	10	20	10	20	50	40	10	-
	Moderate	20	20	20	10	50	30	40	20	30	10	30	10	60	40	20	20	30	30
	Severe	10	-	10	-	30	10	30	-	20	-	50	10	-	-	-	-	10	10
	Total	90	60	80	70	100	70	90	50	70	30	90	40	70	60	70	60	50	40
Discolouration (%)	Mild	-	10	-	10	-	-	10	10	20	10	10	-		10	-	-	-	-
	Moderate	10	-	10	-	-	-	-	-	10	-	-	-	20	10	20	20	20	20
	Severe	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Total	10	10	10	10	-	-	10	10	30	10	10	-	20	20	20	20	20	20
Erosion/Ulcer (%)	Mild	10	20	10	10	40	50	20	40	20	10	10	30	-	10	10	10	10	-
	Moderate	10	10	10	20	10	20	20	-	-	20	10	20	10	10	10	10	-	10
	Severe	20	-	30	10	20		10	-	20	-	50	-	10	-	-	-	20	20
	Total	40	30	50	40	70	70	50	40	40	30	70	50	20	20	20	20	30	30
Friability (%)	Mild	30	20	20	30	50	50	60	30	50	30	40	30	30	30	30	40	20	10
	Moderate	10	10	20	20	20	10	30	-	30	20	10	20	40	30	30	10	60	50
	Severe	10	-	10	-	20	10	-	-	10	-	50	-	10	10	10	10	10	20
	Total	50	30	50	50	90	70	90	30	90	50	100	50	80	70	70	60	90	80
Haemorrhage (%)	Mild	20	30	30	20	50	50	30	20	30	20	40	30	-	30	30	20	20	10
	Moderate	20	-	20	30	20	10	10	-	10	10	10	20	40	-	-	-	60	50
	Severe	10	-	10	-	20	10	20	-	10	-	50	-	-	-	-	-	10	20
	Total	50	30	60	50	90	70	60	20	50	30	100	50	40	30	30	20	90	80
Edema (%)	Mild	10	-	10	-	-	-	20	20	10	10	-	-	10	10	-	10	-	-
	Moderate	-	-	-	-	-	-	10	-	10	-	-	-	-	-	10	-	-	-
	Severe	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Total	10	-	10	-	-	-	30	20	20	10	-	-	10	10	10	10	-	-

With probiotic, there was only little change in clinical, faecal and endoscope score in the IBD dogs of our study. Only 20 per cent reduction in the CIBDAI score (Table 1) and persistent diarrhoea (faecal score 5) post treatment were observed in these dogs (Table 2) (Fig 1). On post treatment endoscopic examination, only minimal changes of the intestinal mucosal lesions compared to pre treatment were recorded (Table 3) (Fig 4). Moreover, there was no significant difference in the endoscopic score before and after treatment (Table 4). This was in contrary to Rossi *et al*. (2014) who observed that high dose probiotic combination was effective for the clinical improvement and faecal consistency with probiotic treatment. This contradiction might be due to the variation in the strain and dose of probiotic used in the present study. Currently there is no published data regarding endoscopic changes after treatment with probiotics in IBD dogs. Moreover, there was increase in liver enzyme levels (Table 5). Though the probiotics lack steroidogenic effect on liver enzymes, the increase may be due to the presence of intestinal mucosal

Table 4: Mean±S.E values of Endoscopic score - Pre and post treatment.

Parameter	Days	Group A (n=10)	Group B (n=10)	Group C (n=10)
Endoscopic	Pre	$5.5^{a}\pm0.72$	$6.5^{a}\pm0.67$	$4.9^{a}\pm0.74$
score	Post	$1.8^{b}\pm0.42$	$1.7^{b}\pm0.29$	$4.1^{a}\pm0.38$
(Composite score)	t value	4.605**	6.162**	0.829^{NS}

**- Statistically highly significant (P<0.01).

*- Statistically significant (P<0.05).

NS-Statistically non significant (P>0.05).

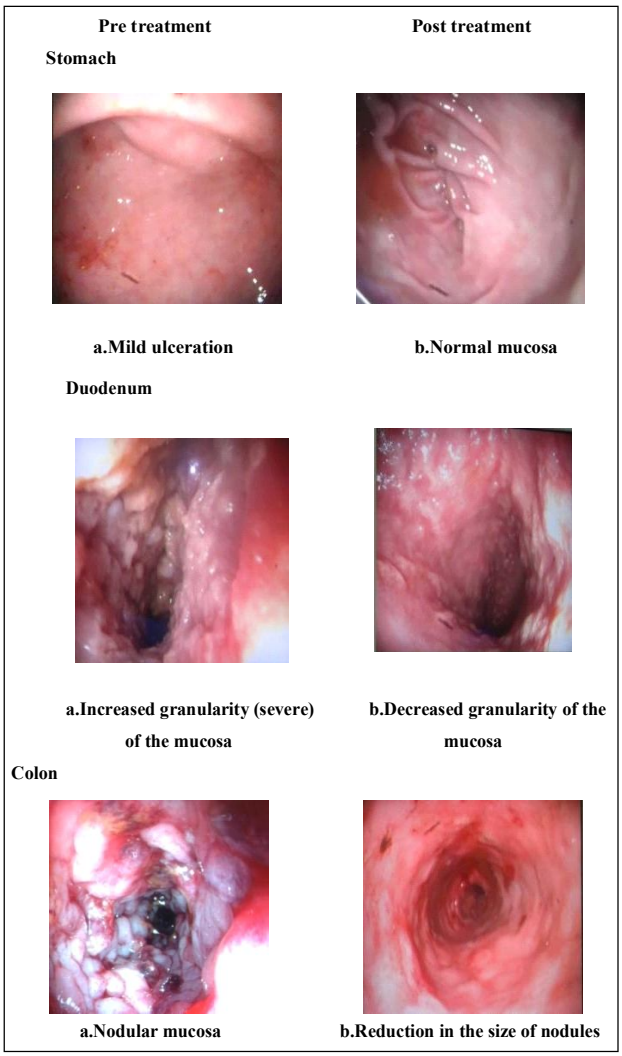


Fig 2: Endoscopic findings pre and post treatment - Group A.

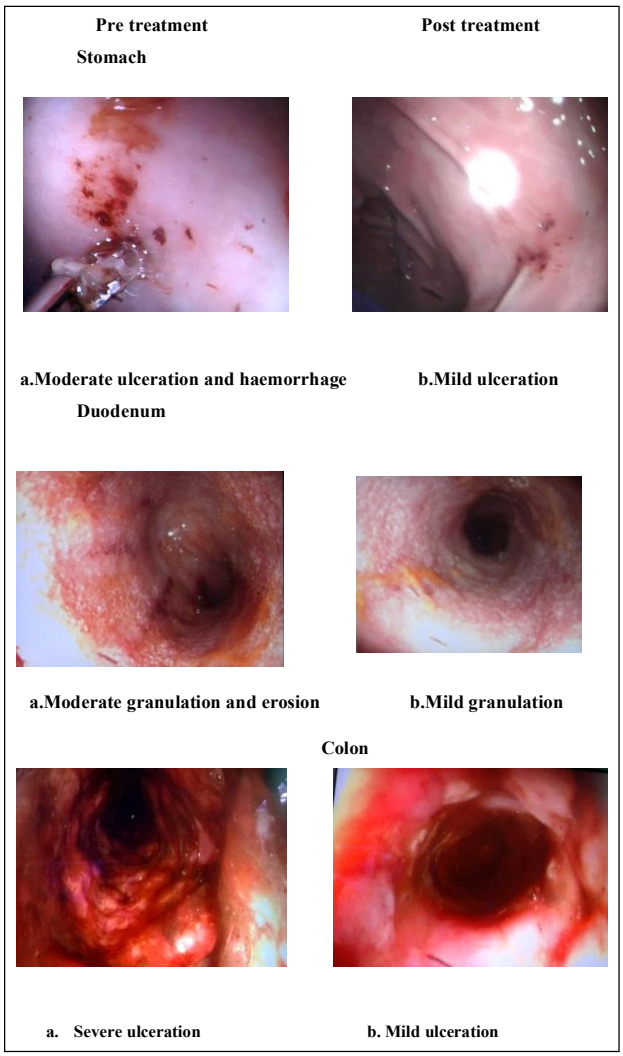


Fig 3: Endoscopic findings pre and post treatment - Group B.

inflammation which was evident on post treatment CIBDAI score and endoscopy.

To compare and evaluate the three therapeutic protocols statistical analysis of the difference values of post and pre treatment CIBDAI values was done. It was observed that both prednisolone and budesonide are equally effective in the management of IBD in dogs (Table 6). These results are comparable with studies of Dye *et al*. (2013) and Pietra *et al*. (2013). Although, these corticosteroids are commonly prescribed for the treatment of IBD in dogs, systemic corticosteroids are often associated with adverse effects. In the present study, there was significant serum alkaline phosphatase and alanine aminotransaminase elevation post treatment in the prednisolone group while in budesonide group a non significant increase was observed (Table 5). This was in agreement with Dye *et al*. (2013) who recorded similar elevations of liver enzymes in both prednisolone and budesonide group. However, in the present study, the documentation of adverse effects is not complete. This may be due to the fact that small numbers of dogs were selected and the study was limited to duration of six weeks. Therefore, to assess the efficacy of budesonide as a maintenance treatment a study of longer duration would be needed. Furthermore, adverse effects related to corticosteroid often become more apparent and less tolerable with a longer duration of treatment. After induction therapy for IBD with prednisolone, gradual dosage tapering is generally recommended to limit adverse effects, but some animals relapse as the dosage is decreased. It is possible that budesonide may be more or less tolerated with long term use than prednisone (Dye *et al*., 2013).

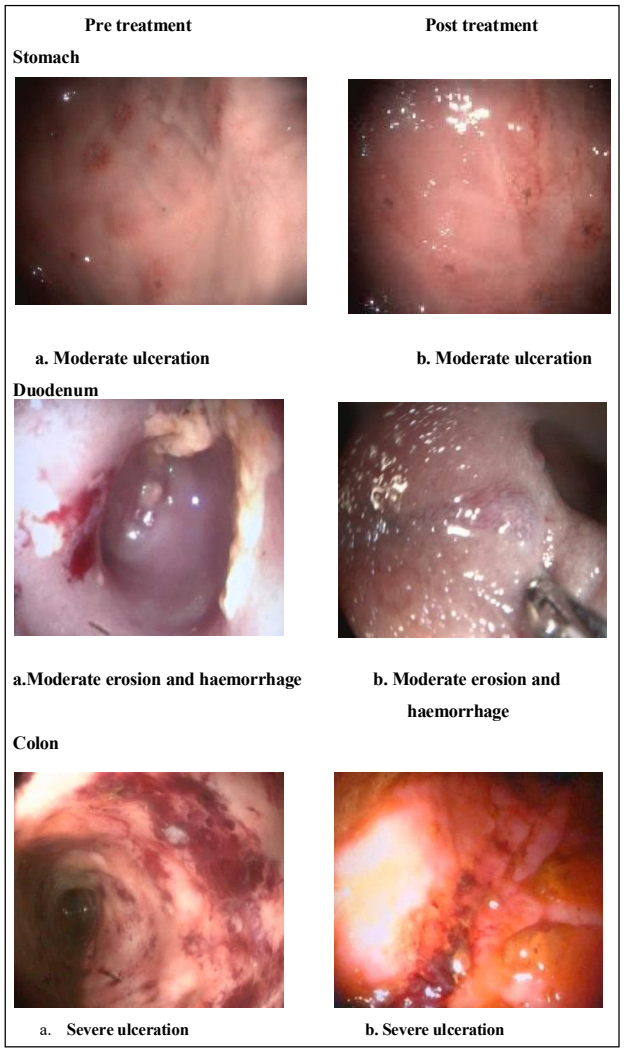


Fig 4: Endoscopic findings-pre and post treatment - Group C.

In our study probiotics were found to be less effective when compared to prednisolone and budesonide in the treatment of IBD (Table 6). In human and veterinary practice, probiotic therapy is becoming increasingly popular. Several studies support the hypothesis that gut microbiota plays a significant role in triggering, maintaining, and amplifying IBD. Specific microbes can be overrepresented in IBD while others seem to be protective. A decrease in microbial biodiversity has been found in mucosa and faeces of IBD patients, along with an increase of fungi. Pre- and probiotics could represent a valid tool to modulate gut microbiota and to cure IBD (Scaldaferri *et al.,* 2013). Denizot *et al*. (2012) stated that the beneficial effects of probiotic intervention on intestinal inflammation could be the result of many different mechanisms, including improvement of colonization resistance, barrier function, metabolic effects, modulation of signal transduction and immune responses. Since, probiotics are becoming a legitimate therapeutic option, the administration of probiotics to dogs with IBD warrants further investigation. It is therefore necessary to determine the probiotic strains

Table 5: Mean±S.E values of biochemical parameters - pre and post treatment.

Parameter	Days	Group A (n=10)	Group II B (n=10)	Group C (n=10)
Serum alkaline	Pre	228.20±37.99	257.70±69.83	233.70±61.47
Phosphatase (IU/L)	Post	452.30±27.51	324.00±29.11	294.20±61.70
	t value	-6.667**	-0.855^{NS}	-1.957^{NS}
Alanine	Pre	47.00±7.62	96.80±20.42	39.7±4.97
Aminotransferase (IU/L)	Post	132.00±11.58	112.80±14.93	59.00±6.95
	t value	-6.830**	-1.350^{NS}	-2.365*

**- Statistically highly significant (P<0.01).
*- Statistically significant (P<0.05).
NS-Statisticallynon significant (P>0.05).

Table 6: Mean±S.E values of CIBDAI score- pre and post treatment difference values.

Parameter	Group A (n=10)	Group B (n=10)	Group C (n=10)	F value
CIBDAI	-3.8[b]±0.44	-5.1[b]±0.43	-2.3[a]±0.30	13.56**

**- Statistically highly significant (P<0.01).

*- Statistically significant (P<0.05).

NS- Statistically non significant (P>0.05).

which have the greatest efficacy, frequency of administration and dose so this can be used as an alternative therapy.

CONCLUSION

Prednisolone and budesonide are equally effective to bring out clinical remission along with metronidazole drug and elimination diet in the management of idiopathic IBD. Probiotics were found less effective in this study. However, considering the apparent important role of microbiota in IBD pathogenesis and steroidogenic side effects observed in conventional treatment, the application of probiotic therapies seems to be a promising alternative. A large scale clinical study is required to utilize probiotic in the management of IBD.

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