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MONITORING THE EFFICACY OF TERLIPRESSIN ACETATE IN DOGS SUFFERING FROM HEMORRHAGIC GASTROENTERITIS (HGE)

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ABSTRACT

In the present study, a therapeutic trial was conducted to assess comparative efficacy of Terlipressin acetate in dogs suffering from hemorrhagic gastroenteritis (HGE). 70 dogs manifesting HGE, presented at teaching veterinary clinic, were selected randomly for the trial. All of them were observed to suffer from moderate dehydration on clinical examination. Terlipressin acetate, dextrose saline infusion 5% were used in combination with antibiotics and symptomatic treatment in the first group and in the second group, the dextrose saline infusion 5%, antibiotics and symptomatic treatment were used, both groups consisting of 35 cases each. The outcome of both treatment groups was evaluated on hematobiochemical parameters, before and after administration of the therapies and compared statistically within and between the two groups. Hematobiochemical parameters of clinically healthy animals were considered as control for comparison. On hematobiochemical examination, no significant alterations were observed in first group and second group. Clinical recovery was faster in the first group than the second group of animals. Laboratory data, efficacies of the Terlipressin acetate were of low importance for recovery in small animals suffering from hemorrhagic gastroenteritis (HGE).

Keywords: Dog, Hemorrhagic gastroenteritis (HGE), Terlipressin acetate.

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INTRODUCTION

Hemorrhagic gastroenteritis (HGE) in dogs is a disease syndrome of unknown cause characterized by acute onset of bloody diarrhea, vomiting and hemoconcentration **(Leipig, 2013)**. HGE is a life-threatening condition due to loss of body fluid and electrolytes along with blood leading to a massive reduction in circulatory volume **(Dow, 1996; Guilford, and Strombeck, 1996; Biffl and Moore, 2000)**. This contributes to high mortality associated with the underlying condition and also with concurrent septic complications **(Burrows,1977; Post and Feldman, 1978; Brown and Otto, 2008; Boag, 2013).** Diarrhea results in fluid and electrolyte losses and, when severe, can lead to hypotension and death **(Argenzio, 1978; Schoeman, 2007 and Unterer *et al.*,2011).** High serum cortisol and low serum thyroxin concentrations at 24 and 48 hours after admission were associated with death in dogs with parvoviral diarrhea **(Schoeman, 2007).**

Causes of HGE, Endoscopic by **Leipig, (2013)**, indicated chronic gastritis, necrotizing inflammation in the small intestine and clostridia antigen-positive bacteria was present in 9/10 cases and in 8/9 cases in the large intestine. The severity of the lesions increased in the caudal part of the intestinal tract.

The exact pathogenesis of a common acute onset of bloody diarrhea and vomiting in dogs is unknown **(Kondo, *et al.*, 1978; Wilhelmsen, 1982; Medinger, 1993; Hess, *et al.*, 1998; Rohrer, *et al.*, (1999); Sasaki, *et al.*, (1999); Dunayer, and Gwaltney-Brant, 2006; Geisen, *et al.*, 2006; Mouser, *et al.*, 2007; Schulz, *et al.*, 2008; and Unterer *et al.*, 2014).** Including idiopathic hemorrhagic gastroenteritis (HGE). **Burrows, (1977); Spielman, and Garvey, (1993)** concluded that, the traditional name for the syndrome has been "hemorrhagic gastroenteritis" (HGE). An association exists between C. perfringens and the occurrence of acute

hemorrhagic diarrhea **(Cave, *et al.*, 2002).** The term "HGE," which implies the involvement of the stomach, should be renamed as "acute hemorrhagic diarrhea syndrome.".

Because of the rapid onset of clinical signs, a type 1 hypersensitivity reaction to food components or bacterial endotoxin has been proposed as an inciting cause in acute diarrhoea **(Hill, 1972);** Canine Parvovirus (CPV) **(Markovich *et al.*, 2012, Duijvestijn *et al.*, 2016)** Canine Coronavirus (CCoV), and β-hemolytic Eschericha coli (hEC), Canine Parvovirus (CPV) and Canine Coronavirus (CCoV), occur frequently together.

Because of the potential bacterial etiology and the risk of sepsis, antibiotics generally are recommended to treat hemorrhagic diarrhea in dogs **(Deitch, (1993).** Frequently, amoxicillin/ clavulanic acid is used as a first antibiotic choice in these cases. This potentiated amino penicillin is a broad-spectrum, time-dependent antibiotic drug that is effective against most Gram-positive, some Gram-negative, and anaerobic bacteria, including potentially enteropathogenic organisms (e.g., some Clostridia spp., Escherichia coli, and Salmonella spp.).

However, in dogs, the frequency and clinical relevance of bacterial translocation and the role of bacteria as inciting agents of HGE, and thus, the necessity of with antibiotics, are not known. Moreover, inappropriate usage of antibiotics can cause disruption of the protective intestinal flora **(Dethlefsen, *et al.*, 2008; and Gronvold, *et al.*, 2010)** post antibiotic salmonellosis, associated with diarrhea, and antibiotic resistance **(Deitch, 1993; Willard, 1998; Baverud, 2002; Costelloe, *et al.*, 2010).**

Oral rehydration therapy has been used successfully for the treatment of mild to moderate dehydration in adults and children as a replacement for IV fluid administration **(Wells, *et al.*, 1987, World Health Organization, 1995; Spandorfer *et al.*, 2005; and Santosham, 2010).** In veterinary medicine, reports of the use of ORT have involved calves with diarrhea (**Cebra, *et al.*, 1998; Goodell, *et al.*, 2012**) horses requiring rehydration **(Marlin, et al., 1998 and Monreal, *et al.*, 1999)** and a small number of working dogs during exercise **(Mazin, *et al.*, 2001**) .No clinical studies for the treatment of dehydration induced by diarrhea in dogs **(Leipig, 2013);** dogs with inflammatory bowel disease (IBD), Cobalamin should be supplemented in all cases with decreased serum cobalamin concentrations **(Allenspach, 2013 and Chandreyee-Sen *et al.*, 2014)** . Using of colloidal infusions may provide a more effective fluid management protocol in the crisis of HGE.

Gastrointestinal system Terlipressin increases the tonus of vasal and extravasal unstriated muscle cells. Due to the increased resistance of the terminal arterial vessels, there is a decreased circulation of the splanchnic nerve. Reduction of the arterial flow leads to a pressure decrease in portal circulation. The simultaneous contraction of the intestinal muscles leads to increased peristalsis. Furthermore, it could be shown that the muscles of the esophageal wall are contracting and thus "ligate" varices experimentally **created (Wells, *et al.*, 2012)**. The use of terlipressin has a slow hemodynamics effect over 2-4 hours. The blood pressure is slightly increased systolically and diastolically. In case of renal hypertonia and general vascular sclerosis, stronger blood pressure increases were observed. Major aim of the study was to determine if Terlipressin acetate has significance in the treatment of HGE, and its influence on hematobiochemical changes.

MATERIALS AND METHODS

Selection of animals

A therapeutic trial was conducted on randomly selected 70 cases (n = 70) of HGE manifesting bloody diarrhea which were presented at, Teaching Veterinary Clinic, Cairo University, Giza, Egypt. All dogs were suffering from frequent vomiting and bloody diarrhea. On examination following the protocol Debasis-Panda, (2008) by skin turgidity test, moistness of mucous membrane, capillary refilling time (CRT), hematobiochemical tests. A group of 10 clinically healthy animals were considered as control for this study.

Study design

A prospective, double random study was designed to evaluate the efficacy of Terlipressin acetate, on the basis of clinical and laboratory findings, which of the 2 therapy methods provides the best therapeutic results.

The cases were divided into two study groups each consisting of 35 cases. In one group of animals Terlipressin acetate, were prescribed with Dextrose Saline infusion 5% antibiotics and symptomatic treatment and in other group Dextrose Saline infusion 5%, antibiotics and symptomatic treatment.
Glypressin® is initially used in human for the treatment of bleeding esophageal varices and Hepatorenal syndrome (HRS).

* Glypressin I + II (Terlipressin acetate) 1 mg. iv injection. Authorization Holder: Ferring GmbH - Germany initially 0,5 mg terlipressin acetate, equivalent to 0,5 vials of Glypressin 1 mg, were

slowly administered intravenously twice daily for 4 successive day.

Total fluid deficit calculated as (in liters') = body weight (kg)×2-5%. The total volume of solutions were infused twice daily for 5 successive days in all the cases in first group along with other supportive therapies. Infusion used in this study was 5% dextrose normal saline (Nile Pharmaceutical company, Egypt), administered at the rate of 20-50 ml/kg bwt./day **(Mensack 2008)** with an infusion rate of 50-60 drops/min.

The animals were observed closely for any adverse reaction while administration of the fluid and vital signs were monitored. Symptomatic therapies including, antiemetic's (metoclopramide hydrochloride and prochlorperazine maleate), H_2-antagonist (ranitidine), coagulants (adenochrome monosemi-carbazide, ethamsylate) after **Dereszynski, et al., (2008)** and antibiotic regimen consisting of amikacin sulphate (10 mg/kg bwt., i/v or i/m, BD), ampicillin (20-25 mg/kg bwt., i/v or i/m, BD), metronidazole (15-20 mg/kg bwt., i/v or i/m, BD) were provided to both group of animals **(Boag, 2013).**

Clinical and hematobiochemical parameters were noted in both groups on the day of the presentation and day 7. Hematobiochemical parameters of the control group dogs were considered as a reference to compare with the after treatment values of diseased animals for assessing improvement towards normalization.

Blood sampling and processing

Blood samples (approximately, 2 ml) were collected from each dog before the start of any treatment by vein puncture of both cephalic or recurrent tarsal vein, and using heparin (10 IU/ml of blood) as anticoagulant. Approximately, 1 ml of blood was kept for analysis of blood and rest of the sample was processed for separation of serum. Blood samples were centrifuged at 2000 rpm for 5 min in centrifuge to separate serum. The serum was collected in to a clean Eppendorf tube.

Hematobiochemical examination

Table (1) shows the blood and plasma biochemical in fluid therapy group of dogs at day zero. Erythrocytes, Hematocrit, Thrombocytes, Leukocytes, Granulocytes, Stab cell, Segmented Lymphocytes, Monocytes, Eosinophil, Basophile, Glucose, Creatinine, Total protein, Albumin, Aspartate Aminotransferase, Alanine Aminotransferase, Amylase, Lipase, Sodium, Potassium and Chloride Table (2) shows the blood and plasma biochemical in fluid therapy group of dogs at day 7.

Statistical Analysis

The differences were made with one-factor Variance analysis (One way ANOVA) and post-hoc analysis by LSDA algorithm Investigated.

RESULTS

Median (range) age of dogs with hemorrhagic gastroenteritis was 1,3 years old (0.8 to 4 years old). The study included 47 males, and 23 females. Dogs were of large breeds. No significant differences were found between treatment groups concerning severity of clinical signs, over the course of disease, was observed. Clinicopathologic data (Table 1), (Table 2). of hemorrhagic gastroenteritis may have packed cell volumes as high as 75%. Severe intestinal blood loss can also lead to anemia and panhypoproteinemia. Leukocytosis with immature bands is a common finding with systemic infection. Leukocytosis with lymphopenia and eosinopenia (stress leukogram).

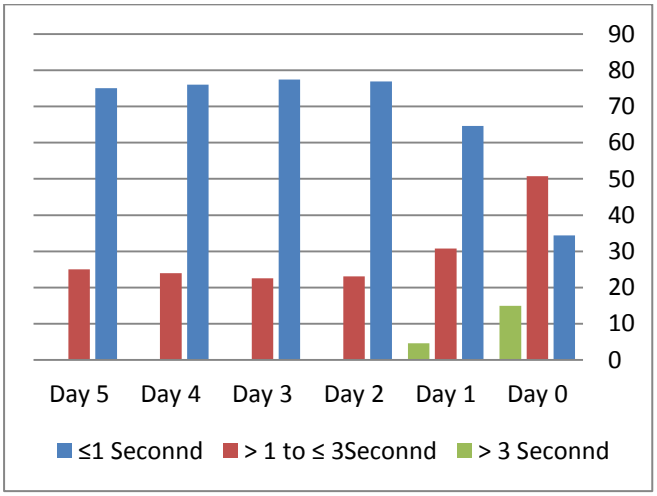

Diagram 1: Capillary refilling time changes in Terlipressin acetate group.

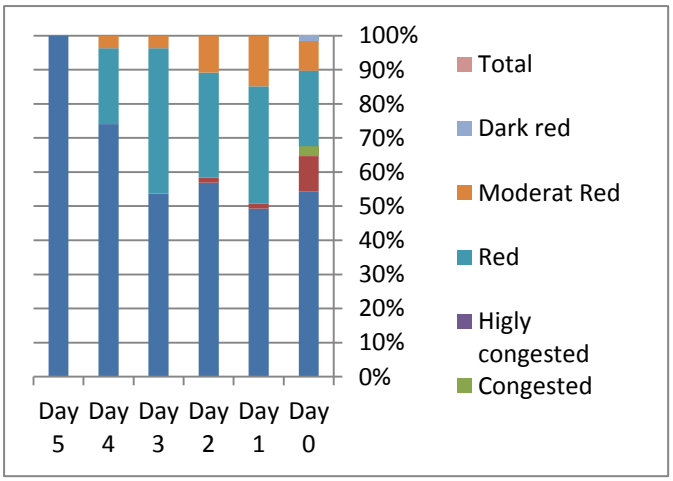

Diagram 2: Mucous membranes color changes in Terlipressin acetate group

Table 1: Blood and plasma biochemical in terlipressin acetate group of dogs at day zero.

Parameter	Unit	N	Min	Max	M. Value	SE
Erythrocytes	/µl	43	10430000	8500372	779000	428781
Hematocrit	%	70	55	82	62.19	1.33
Thrombocytes	/µl	41	156000	618000	310097.6	24592.81
Leukocytes	/µl	51	7680	30140	14900.39	1160.89
Granulocytes	/µl	27	1700	21000	11040.74	1078.31
Stab cell	/µl	17	0.08	2602	314.82	158.58
Segmented	/µl	17	5021.06	27306.84	11847.35	1218.72
Lymphocytes	/µl	34	690.2	4600	2303.79	264.06
Monocytes	/µl	17	353.1	1417.68	889.06	75.20
Eosinophil	/µl	17	0.12	470.8	154.44	31.19
Basophile	/µl	17	0.12	542.52	96.09	29.28
Glucose	mg/dl	45	30	418	106.58	12.57
Creatinine	mg/dl	51	0.4	1.3	0.77	0.05
Total protein	g/dl	67	5	12	7.02	0.24
Albumin	g/dl	20	1.7	4.22	3.34	0.15
AST	U/l	6	3	79	41.83	6.85
ALT	U/l	50	10	167	54.89	8.48
Amylase	U/l	34	232	2493	642.68	86.27
Lipase	U/l	31	30	890	173	41.89
Sodium	mmol	29	79	150	140.1	3.39
Potassium	mmol	41	2	4.9	3.94	0.11
Chloride	mmol	26	95	128	113.54	1.76

Table 2: Blood and plasma biochemical in Terlipressin acetate group of dogs at day 7.

Parameter	Unit	N	Min	Max	M. Value	SE
Erythrocytes	/µl	36	4360000	11390000	7040000	231692
Hematocrit	%	63	36	75	48.1	1.53
Thrombocytes	/µl	26	61100	509000	278888	26135.23
Leukocytes	/µl	49	5830	35710	14173	1241.12
Granulocytes	/µl	3	6900	13900	10300	787.47
Stab cell	/µl	12	0.09	1772	284	136.06
Segmented	/µl	12	3941	17286	9566	969.08
Lymphocytes	/µl	14	1175	4954	2692	228.86
Monocytes	/µl	12	239	1347	729	82.76
Eosinophil	/µl	12	0.15	1576	564	98.40
Basophile	/µl	12	0.1	194	43	60.3
Glucose	mg/dl	43	36	118	89	3.68
Creatinine	mg/dl	43	0.4	1.3	0.76	0.05
Total protein	g/dl	44	4.38	7.8	5.99	0.17
Albumin	g/dl	65	1.9	3.8	3.07	0.09
AST	U/l	39	15	135	33.3	6.44
ALT	U/l	21	18	126	53.7	5.93
Amylase	U/l	40	62	4560	950.1	199.36
Lipase	U/l	43	28	2358	213.37	89.16
Sodium	mmol	9	145	153	147.67	0.61
Potassium	mmol	38	2.7	4.5	3.8	0.08
Chloride	mmol	5	112	119	114.2	0.62

DISCUSSION

There was wide variation in the severity of clinical signs, and some dogs with HGE were presented as medical emergencies. Marked clinical improvement usually was observed within the first 24–48 hours. Clinical treatment response was less improved in patients of second group. This leads to the assumption that, terlipressin acetate with aggressive IV fluid therapy, seems to be more important in the treatment of dogs with HGE. With adequate supportive therapy and close patient monitoring, the mortality rate is low our results agree with finding of **Unterer, (2011); Hackett, (2011), and Reineke *et al.*, (2013)** also state that electrolyte solution for oral administration is safe and effective treatment with sudden onset of hemorrhagic diarrhea significantly less expensive than (IVT) IV treatment and, less demanding for veterinary staff and could potentially be initiated or maintained by the dog owner.

Terlipressin (Tri-glycyl-lysine-vasopressin)

Bayram, *et al.*, (2012) found that, is a long-acting vasopressin analogue, which was produced for the pharmacologic treatment of esophageal variceal hemorrhage **(Jackson, 2006).** Clinical and experimental studies have also revealed that terlipressin leads to a significant improvement in mean arterial blood pressure in patients with catecholamine- resistant septic shock **(Delma, *et al.*, 2005).** However, there are only a few studies regarding the application of terlipressin in human beings in hemorrhagic cases, and a randomized controlled study of this treatment method has yet been conducted. This study was designed to evaluate the effects of terlipressin vs controlled fluid resuscitation on hemodynamic variables and abdominal bleeding in a rat model of uncontrolled hemorrhage via liver injury.

Hematobiochemical examination

In contrast to clinical finding Blood and plasma biochemical no significant alterations were observed. Enteritis resulting in sudden onset of hematochezia in dogs can have several causes, including but not limited to infection with enteropathogens, dietary hypersensitivity, ischemia within the gastrointestinal tract, and systemic disease. In diarrheal diseases, a derangement in the secretory-absorptive processes of the gastrointestinal tract develops through osmotic or secretory mechanisms, resulting in water and electrolyte losses. Damage to the epithelial intestinal barrier, such as that caused by many enteropathogens, may lead to a decrease in absorptive capabilities **(Argenzio, 1978; Ooms, and Degryse,1986).**

When the absorptive capacity of the intestines is overwhelmed, osmotically active particles retain water in the intestinal lumen, resulting in excessive fecal water loss **(Argenzio, 1978; Ooms, and Degryse, 1986)** ; such water loss can result in dehydration and potentially hypovolemia when oral intake of water is not adequate or the patient is vomiting. Hypokalemia can be a complication of vomiting and diarrhea because of the decrease in oral intake and gastrointestinal tract loss of potassium **Whipp, (1978).** Serum activities of liver enzymes typically reflect cellular changes and usually correspond with the histologic features of liver injury **Vespb, (1986). Allenspach, (2013)** A serum albumin concentration of less than 2 g/L is an indicator of poor prognosis in dogs.

Symptomatic treatment

Dog's gastroenteritis has been reported to be the highest in younger ages **(Houston *et al.*, 1996).** Trace elements are integral part of cellular antioxidant system and elements like copper, zinc and selenium participate in cellular defense against oxidants **(Klotz *et al.*, 2003; Munoz *et al.*, 2007)**, Significantly increased level of blood copper was observed in dogs suffering from gastroenteritis. Increased level of copper in the blood of affected animals might be due to increased inflammatory response as copper is an integral part of protein ceruloplasmin and its level rises in acute phase response. decreased level of blood due to loss of blood. Zinc is a component of Cu–Zn Superoxide dismutase **(Bray and Bettger, 1990)** that converts the superoxide radicals to hydrogen peroxide, which is further decomposed by catalase into water and oxygen. low level of blood zinc.

There are reports indicating significant effect of oral zinc supplementation on morbidity in acute diarrhea in children **(Sazawal *et al.*, 1997; Wingertzahn *et al.*, 2003).** There are several reports supporting the hypothesis that host micronutrient status may contribute towards disease pathogenesis **(Beck *et al.*, 2004)** and nutritionally compromised hosts are more susceptible to viral infection **(Beck and Levander, 1998). Khoo *et al.*, (2005)** showed that animals on high antioxidant foods had significantly increased titers and memory cells during canine parvovirus and canine distemper virus vaccination.

Antimicrobials

Results agree with **Hackett, (2011)** as hemorrhagic diarrhea, should have an intravenous catheter placed to receive parenteral fluids and antibiotics. However **Unterer, (2011)** found that, no documented evidence that patients with HGE truly have an increased risk for bacterial

translocation or sepsis, and the efficacy of antibiotic therapy in the treatment of HGE has not been demonstrated. There is evidence that resistance to antimicrobials is increasing among bacteria isolated from pets **(Lloyd, 2007; Bibbal, *et al.*, 2009; Oluoch, *et al.*, 2001.**Thus, unnecessary antibiotic treatment should be avoided. In addition, antimicrobial therapy can disrupt the normal microbial flora, which is important for defense against pathogens, (**Suchodolski, *et al.*, 2009; Gronvold, *et al.*, 2010).**

Enteric C. perfringens infection and CPE Clostridium perfringens enterotoxin production have been proposed to cause acute gastrointestinal disease **(Bartlett, *et al.*, 1972; Weese, *et al.*, 2001; Marks, *et al.*, 2002)** and hemorrhagic diarrhea **(Prescot et al., 1978; Sasaki, *et al.*, 1999; Cave, *et al.*, 2002; McKenzie, 2010). Marks, and colleagues, (2002)**, changes in the intestinal environment of dogs with diarrhea promote increased proliferation and transient overgrowth of enterotoxigenic strains of C. perfringens. This is supported by the fact that amoxicillin/clavulanic treatment was not associated with a better clinical response than placebo.

CONCLUSIONS

In some dogs with Hemorrhagic gastroenteritis (HGE), Terlipressin acetate with aggressive IV fluid therapy, may change the case outcome or time to recovery. The challenge to the veterinary clinician is to replace the lost fluids, electrolytes, and proteins while preventing septic complications. It is vital to monitor the major organ function and treat the primary disease and secondary organ dysfunction in a timely manner.

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